ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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SPECIAL ARTICLE

Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO–ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS

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The most recent version of the European Society for Medical Oncology (ESMO) consensus guidelines for the treatment of patients with metastatic colorectal cancer (mCRC) was published in 2016, identifying both a more strategic approach to the administration of the available systemic therapy choices, and a greater emphasis on the use of ablative techniques, including surgery. At the 2016 ESMO Asia Meeting, in December 2016, it was decided by both ESMO and the Japanese Society of Medical Oncology (JSMO) to convene a special guidelines meeting, endorsed by both ESMO and JSMO, immediately after the JSMO 2017 Annual Meeting. The aim was to adapt the ESMO consensus guidelines to take into account the ethnic differences relating to the toxicity as well as other aspects of certain systemic treatments in patients of Asian ethnicity. These guidelines represent the consensus opinions reached by experts in the treatment of patients with mCRC identified by the Presidents of the oncological societies of Japan (JSMO), China (Chinese Society of Clinical Oncology), Korea (Korean Association for Clinical Oncology), Malaysia (Malaysian Oncological Society), Singapore (Singapore Society of Oncology) and Taiwan (Taiwan Oncology Society). The voting was based on scientific evidence and was independent of both the current treatment practices and the drug availability and reimbursement situations in the individual participating Asian countries.

Key words: colorectal cancer, Pan-Asian, consensus, clinical practice guidelines

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the fourth most common cause of cancer death worldwide [1]. In 2012, in Europe there were an estimated 447 000 new cases of CRC with 215 000 deaths, in Asia there were an estimated 607 000 new cases of CRC and 332 000 deaths, and worldwide there were 1.4 million new cases and 694 000 deaths [1].

Significantly, both the incidence of, and deaths from, CRC have increased in most countries of the Asia-Pacific region over recent decades, probably due to changes in diet associated with urbanisation, and continue to rise [2]. In the case of Japan, for example, the incidence and mortality rates for CRC increased markedly between 1958 and the mid-1990s, in parallel with economic growth, but they have since plateaued and today may even have decreased slightly [1, 3, 4]. Thus, CRC represents a major and increasing healthcare challenge across the region.

Guidelines for the screening, and treatment and management of patients with colon and rectal cancers in Asia have been published previously [5–8], and the European Society for Medical Oncology (ESMO) consensus guidelines for the management of patients with metastatic CRC (mCRC) have recently been updated [9]. A decision was taken by the European and Japanese societies for medical oncology, ESMO and JSMO, respectively, that the latest ESMO consensus guidelines for the management of patients with mCRC should be adapted for patients of Asian ethnicity. Consequently, at the ESMO Asia meeting in Singapore 16–19 December 2016, a meeting was convened with the Presidents and/or appointed representatives of the Chinese Society of Clinical Oncology (CSCO), the Korean Association for Clinical Oncology (KACO), the Malaysian Oncological Society (MOS), the Singapore Society of Oncology (SSO) and the Taiwan Oncology Society (TOS) together with those of the JSMO and the ESMO to formally agree and launch the project. As a result, a one-day working meeting was held on 30 July 2017 in Kobe Japan immediately after the 15th Annual Meeting of the JSMO, to adapt and update the recent ESMO consensus guidelines for the management of patients with mCRC [9] for use in the treatment and management of Asian patients with mCRC.

Methodology

Composition of the expert panel

An international panel of experts was selected based on their demonstrable knowledge of the treatment and management of patients with CRC in terms of publications and/or their participation in the development of national or international treatment guidelines. More specifically this included seven expert members of the JSMO, six expert members of the ESMO, two experts from the United States who were also ESMO members, and two experts each from the oncological societies of China (CSCO), Korea (KACO), Malaysia (MOS), Singapore (SSO) and Taiwan (TOS).

Provisional statements

Slide sets based on the preformulated topics, the 21 recommendations and the consensus recommendations on the use of anticancer drugs in the first- and subsequent-line treatment of patients with mCRC included in the latest ESMO consensus guidelines [9] were circulated in February 2017 to all participating Asian experts to gather their comments/input for each recommendation with the specific focus based on the data available from Asian studies, Asian patient subsets of international studies and expert opinion. The Asian experts were specifically asked: 'Can this recommendation be adapted in your country?' The experts were also asked to provide details of the reasons for their response, and references in support of their decisions. These responses were then collated by the meeting organisers (TY and JYD). A second survey (May 2017) before the on-site meeting in Japan asked the Asian experts for their responses to a specific series of questions with regard to the treatment of patients with left-sided versus right-sided colon cancer and the details of the approval and reimbursement of the drugs specified in each of the ESMO recommendations, as well as the availability of biomarker testing, in their individual countries.

Voting process

A modified Delphi process was used to develop each individual statement before the discussion and the voting process. Experts from Asia only, were asked to vote based on the evidence available, on a scale of A to E, where A=accept completely, B=accept with some reservation, C=accept with major reservations, D=reject with some reservation and E=reject completely (supplementary Table S1, available at *Annals of Oncology* online). An adapted version of the 'Infectious Diseases Society of America-United States Public Health Service Grading System' [10] was used to define both the level of evidence and strength of each recommendation proposed by the group (supplementary Table S1, available at *Annals of Oncology* online), and are given in the text in square brackets after each recommendation, together with details of the levels of agreement. Most statements on the level of agreement were based on peer-reviewed manuscript data or peer-reviewed abstract data from both Asian and Western trials as appropriate, although statements made based on expert opinion were also considered to be justified standard clinical practice by the experts and the JSMO and ESMO faculty. The Asian experts were asked to make their decisions based on the available 'scientific' evidence rather than on some of the current practices in their respective countries, and also, independently of the approval and reimbursement status of certain drugs in their individual countries. Details of the methodology for the final voting and consensus statements are provided in supplementary Data S1, available at *Annals of Oncology* online.

Results

In the initial pre-meeting survey, experts representing six Asian countries (Japan, China, Korea, Malaysia, Singapore and Taiwan) reported on the applicability of the 21 ESMO recommendations and the 17 ESMO consensus recommendations, grouped into 3 treatment categories, presented in the 2016 ESMO consensus guidelines [9]. Agreement was not reached between countries on ESMO recommendations 2b, 4a and c, 5, 6a and b, 7b and c, 8d, 12c and d, 13b, 15a, b and c, 16a, 17, 18a, b

and c, 19a, b, c and d, 20a, b and c, 21b and c and consensus recommendations A1a, b and e, A2a and b, B1a and c. At the face to face meeting in Kobe, Japan, 12 Asian experts in the treatment of CRC, voted on these recommendations. Voting on 'recommendations 1, 3, 9, 10, 11 and 14' was not required. The final levels of agreement and levels of evidence and strength of support recorded for each ESMO recommendation by the Asian panel members are provided in the text below for each of the 21 recommendations, and for each of the ESMO consensus statements. In parallel, the final voting patterns of the representatives of each of the participating regions for the 21 ESMO recommendations and 17 ESMO consensus recommendations are presented in supplementary Tables S2–S5, available at *Annals of Oncology* online. Where changes to the original text have been made these are emphasised in bold text and reference made to the change in the text as appropriate. The impact of the location of the primary tumour (left- versus right-sided) on any treatment decisions [11], was also considered at the face-to-face meeting, as described (supplementary Data S1, available at *Annals of Oncology* online), and was included in the final recommendations.

Molecular pathology and biomarkers

ESMO recommendations 1–3

The Pan-Asian panel of experts agreed with and accepted completely [A=100%] the ESMO recommendations on 'tissue handling, recommendation 1' (Table 1 and supplementary Table S2, available at *Annals of Oncology* online), although there was some discussion about the timing of the cutting of the sections for biomarker testing amongst the experts from China, Korea and Malaysia before arriving at this agreement, and it was recognised that in some public hospitals the fixation time might exceed 48 h in certain situations. The decisions were supported by three Japanese studies [12–14], the Japanese Society of Pathology [15], two European references [16, 17] and the Chinese (CSCO) 2017 guidelines [18]. The experts also agreed [A=100%] with the involvement of the pathologist in the 'selection of specimens for biomarker testing' indicated for 'recommendation 2a' (Table 1 and supplementary Table S2, available at *Annals of Oncology* online), although support for the recommendation about macro-dissection was not initially agreed by the experts from China as the value of macro-dissection in Chinese hospitals could not be verified. There was total agreement [A=100%] on 'recommendation 3' based on Asian publications [19–21] (Table 1 and supplementary Table S2, available at *Annals of Oncology* online).

ESMO recommendation 4 with revision: RAS testing

4a. *RAS* mutational status is a predictive biomarker for therapeutic choices involving epidermal growth factor receptor (EGFR) antibody therapies in the metastatic disease setting [A=100% and I, A].

- *RAS* testing should be carried out on all patients at the time of diagnosis of mCRC [A=100% and I, A].

4b. *RAS* testing is mandatory before treatment with the EGFR-targeted monoclonal antibodies cetuximab and panitumumab [A=100% and I, A].

4c. A network of arrangements should be established to ensure the rapid and robust transit of tissue samples from referral centres to testing laboratories, to minimise the turnaround time and avoid delays in having this information available for all patients with mCRC [A=100%].

4d. Primary or metastatic colorectal tumour tissue can be used for *RAS* testing (see also 'recommendation 3') [A=100%].

4e. *RAS* analysis should include at least *KRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and *NRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117) [A=100%].

4f. Turnaround time for *RAS* testing should be $\leq$**10** working days from the time of receipt of the specimen by the testing laboratory to the time of issuing of the final report, for >90% of specimens. The level of agreement was 100% [A=100%], subject to changing the turnaround time for tumour *RAS* testing from $\leq$7 to $\leq$10 days.

4g. Validation (or verification, where more applicable) of *RAS* testing assays should be carried out and recorded before their implementation in clinical use. Laboratory audit mechanisms should be in place [A=100%].

4h. Laboratories providing *RAS* testing of colorectal tumours should demonstrate their successful participation in a relevant external quality assessment scheme, and be appropriately accredited [A=100%].

The panel of Asian experts agreed completely [A=100%] with the ESMO guidelines 'recommendation 4' above, that *RAS* testing should be carried out on the tumours of all patients with mCRC at the time of diagnosis. This opinion was based on retrospective studies in Japanese [22, 23], and other Asian [24, 25] patients with mCRC, which confirmed in Asian patients the observations made in Western studies [26–39], that patients with tumour *RAS* mutations were unlikely to benefit from EGFR antibody therapies. There is no difference in the prevalence of *RAS* mutations between the tumours of Western patients with mCRC and those of Japanese patients with mCRC [40, 41]. Thus, mandatory *RAS* testing of patients with mCRC before treatment with EGFR antibody therapy is already recommended in the JSMO guidelines [13], and in China (CSCO guidelines) [18], Korea [42], Malaysia (as per the ASCO guidelines [43]), Singapore (as per the ESMO guidelines [9]), and Taiwan (National Health Administration of Taiwan), tumours from patients with mCRC are tested for both *KRAS* and *NRAS* mutations as per 'ESMO recommendation 4e'. It was the opinion of the Japanese experts, that where appropriate, chemotherapy for mCRC patients should be commenced within 2 weeks of diagnosis. Therefore, the testing of the *RAS* mutational status of patient tumours should be completed within 2 weeks, i.e. ~7 days from the time of receipt of the specimen by the central laboratory to the time of reporting. The Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines [7] recommend that *RAS* mutation testing should be carried out, according to a standard recognised testing procedure, in laboratories well-qualified to perform both the testing procedure and specimen management [7]. Both concepts, ESMO 'recommendations 4f and 4g' (supplementary Table S2, available at *Annals of Oncology* online), were supported by China, Korea, Malaysia,

Table 1. Summary of Asian recommendations including consideration of left- versus right-sided primary tumour location

Molecular pathology and biomarkers

Recommendation 1: tissue handling

1a. Fixation with 10% neutral buffered formalin (4% formaldehyde) is recommended [V, A].

1b. Fixation time should be no <6 h, and no >48 h in duration. In the case of microwave-enhanced fixation the quality of both nucleic acids and proteins must be verified [IV, A].

1c. Sections for biomarker testing should ideally be cut immediately before analysis [IV, A].

Recommendation 2: selection of specimens for biomarker testing

2a. The primary pathologist should review all available tumour specimens to select those that are most suitable for biomarker analyses [IV, A].

2b. Enrichment of samples by macro-dissection to maximise tumour cell content (>50%) before DNA extraction is recommended [III, A].

Recommendation 3: tissue selection

3a. Tissue from either the primary tumour or a liver metastasis may be used for *RAS* mutation testing [III, A].

3b. Other metastatic sites such as lymph node or lung metastases may be used only if primary tumour or liver metastases samples are not available [II, B].

Recommendation 4 with revision: RAS testing

4a. RAS mutational status is a predictive biomarker for therapeutic choices involving EGFR antibody therapies in the metastatic disease setting [I, A].

- *RAS* testing should be carried out on all patients at the time of diagnosis of mCRC [I, A]

4b. RAS testing is mandatory before treatment with the EGFR-targeted monoclonal antibodies cetuximab and panitumumab [I, A].

4c. A network of arrangements should be established to ensure the rapid and robust transit of tissue samples from referral centres to testing laboratories, to minimise the turnaround time and avoid delays in having this information available for all patients with mCRC.

4d. Primary or metastatic colorectal tumour tissue can be used for *RAS* testing (see also *Recommendation 3*).

4e. *RAS* analysis should include at least *KRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and *NRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117).

4f. Turnaround time for *RAS* testing (expanded *RAS* analysis) should be ≤**10** working days from the time of receipt of the specimen by the testing laboratory to the time of issuing of the final report, for >90% of specimens.

4g. Validation (or verification, where more applicable) of *RAS* testing assays should be carried out and recorded before implementation in clinical use. Laboratory audit mechanisms should be in place.

4h. Laboratories providing *RAS* testing of colorectal tumours should demonstrate their successful participation in a relevant external quality assessment scheme, and be appropriately accredited.

Recommendation 5 with revision: BRAF testing

5. Tumour *BRAF* mutation status **(V600E)** should be assessed alongside the assessment of tumour *RAS* mutational status for prognostic assessment [I, B].

Recommendation 6 with revision: tumour mismatch repair (MMR) testing

6a. **Immunohistochemistry (IHC) tests for MMR proteins or PCR tests for microsatellite instability (MSI)** in the metastatic disease setting can assist clinicians in genetic counselling [II, B].

6b. **Tumour MMR** testing has strong predictive value for the use of immune check-point inhibitors in the treatment of patients with mCRC [II, B].

Recommendation 7 with revision: biomarkers of chemotherapy sensitivity and toxicity

7a. DPD testing before 5-FU administration remains an option but is not routinely recommended [II, D].

7b. UGT1A1 phenotyping remains an option and **is recommended to be 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].
*__Depending on prevalence of UGT1A1 polymorphisms per country a lower irinotecan threshold dose for *UGT* genotyping may be used__

7c. ERCC1 expression cannot be recommended for use as a biomarker for treatment decisions involving the use of oxaliplatin in routine clinical practice, but could be included prospectively in clinical trials [III, D].

7d. TS activity and *TSER* genotyping are not recommended for use in clinical practice [II, D].

Recommendation 8: emerging biomarkers

8a. Detection of mutations in *PIK3CA*, exon 20 is optional [II, D].

8b. Evaluation of PTEN loss by IHC is not recommended [V, D].

8c. Evaluation of the levels of the EGFR ligands amphiregulin, epiregulin and transforming growth factor-α, is not recommended [II, D].

8d. Evaluation of levels of EGFR protein expression is not recommended [II, E].

8e. Evaluation of *EGFR* amplification and copy number and *EGFR* ectodomain mutations are not recommended [IV, D].

8f. Evaluation of *HER2* amplification or *HER2* activating mutations are currently not recommended outside clinical research.

8g. Evaluation of HER3 and MET receptor overexpression are not recommended [IV, D].

Continued

Recommendation 9: emerging technologies

9a. Although CTC number correlates with prognosis in patients with mCRC, the clinical utility of CTC assessments is not yet clear and therefore cannot be recommended [IV, D].

9b. The utility of ctDNA to guide treatment decisions is currently under investigation in clinical trials, but cannot yet be recommended in routine practice [V, D].

9c. Whole genome, whole exome and whole transcriptome analysis should be carried out only in a research setting [V, D].

Local ablative treatment, including surgery and the management of patients with oligometastatic disease (OMD)

Recommendation 10: OMD

10a. For patients with OMD, systemic therapy is the standard of care and should be considered as the initial part of every treatment strategy (exception: patients with single/few liver or lung lesions, see below).

10b. The best local treatment should be selected from a 'toolbox' of procedures according to disease location, treatment goal ('the more curative the more surgery'/higher importance of local/complete control), treatment-related morbidity and patient-related factors such as comorbidity/ies and age [IV, B].

Recommendation 11: imaging in the identification and management of disease

11a. Imaging should comprise firstly an abdominal/pelvic and thoracic CT scan and, in the case of doubt, a second method such as US (CEUS), MRI or PET/CT scan depending on the location of the metastases. US may be helpful to characterise liver metastases, MRI liver, peritoneal or pelvic metastases and PET/CT extrahepatic disease [IV, B].

11b. A stepwise imaging approach is the recommended policy, in relation to the therapeutic possibilities, rather than the use of all imaging modalities in all patients [V, B].

Recommendation 12 with revision: perioperative treatment

12a. Both, technical criteria for resection and prognostic considerations define the need for systemic perioperative therapy [IV, B].

12b. In patients with clearly resectable disease and favourable prognostic criteria, perioperative treatment may not be necessary and upfront resection is justified [I, C; consensus >75%].

12c. In patients with technically resectable disease where the prognosis is unclear or probably unfavourable, perioperative combination chemotherapy (**a fluoropyrimidine plus oxaliplatin**) should be administered [I, B; consensus >75%].

12d. Targeted agents should not be used in **patients with** resectable **metastases during perioperative therapy** [II, E].

12e. In situations where the criteria for prognosis and resectability are not sharply defined, perioperative therapy should be considered [IV, B]. Patients with synchronous onset of metastases should be allocated to this group and therapeutic pathway.

12f. **In patients who have not received preoperative chemotherapy, with favourable oncological and technical (surgical) criteria, there is no strong evidence to support the use of adjuvant chemotherapy [II, C], whereas patients with unfavourable criteria may benefit [III, B]. Postoperative treatment with a fluoropyrimidine plus oxaliplatin is recommended [IV, B].**

12h. Decision-making should include patients' characteristics and preferences [A=100% and IV, B].

Recommendation 13 with revision in consideration of primary tumour location: conversion therapy

13a. In potentially resectable patients (if conversion is the goal), a regimen leading to high response rates and/or a large tumour size reduction (shrinkage) is recommended [II, A].

13b. There is uncertainty surrounding the best combination to use as only a few trials have addressed this specifically:

- In patients with *RAS* wt disease a cytotoxic doublet plus an anti-EGFR antibody seems to have the best benefit risk/ratio, although the combination of FOLFOXIRI plus or minus bevacizumab may also be considered and, to a lesser extent, a cytotoxic doublet plus bevacizumab [II, A]
- In patients with *RAS* mutant disease: a cytotoxic doublet plus bevacizumab or FOLFOXIRI plus or minus bevacizumab [II, A]
- **Consideration needs to be given to new data on the impact of primary tumour location**

13c. Patients must be re-evaluated regularly in order to prevent the overtreatment of resectable patients as the maximal response is expected to be achieved after 12–16 weeks of therapy in most patients.

Recommendation 14: ablative techniques

14. Despite the lack of more available prospective data, this strategic treatment approach should be evaluated and pursued further in suitable patients [II, B].

Recommendation 15: local ablation techniques

15a. In patients with unresectable liver metastases only, or OMD, local ablation techniques such as thermal ablation or high conformal radiation techniques (e.g. SBRT, HDR-brachytherapy) can be considered. The decision should be taken by a MDT based on local experience, tumour characteristics, and patient preference [IV, B].

15b. In patients with lung only or OMD of the lung, ablative high conformal radiation or thermal ablation may be considered if resection is limited by comorbidity, the extent of lung parenchyma resection, or other factors [IV, B].

15c. SBRT is a safe and feasible alternative treatment of oligometastatic colorectal liver and lung metastases in patients not amenable to surgery or other ablative treatments [IV, B].

15d. RFA can be used in addition to surgery with the goal of eradicating all visible metastatic sites [II, B].

Continued

Recommendation 16 with revision: Embolisation

16a. For patients with liver-limited disease failing the available chemotherapeutic options
- Radioembolisation with yttrium-90 microspheres **can** be considered [II, **C**]
- Chemoembolisation may be also considered as a treatment option [IV, B].

16b. Radioembolisation (and chemoembolisation) of colorectal liver metastases in earlier treatment lines may be interesting as 'consolidation treatment' but should be limited to clinical trials.

Recommendation 17 with revision: cytoreductive surgery and HIPEC

17. Complete cytoreductive surgery and HIPEC can be considered for patients with limited peritoneal metastases in centres which are experienced in the use of HIPEC [II**I**, **C**].

Treatment of metastatic disease

Recommendation 18 with revision in consideration of primary tumour location: first-line systemic therapy combinations according to targeted agent used

18a. Biologicals (targeted agents) are indicated in the first-line treatment of most patients unless contraindicated [I, A]
- **Consideration also needs to be given to new data on the impact of primary tumour location.**

18b. **When used** the VEGF antibody bevacizumab should be **administered** in combination with:
- The cytotoxic doublets FOLFOX/CAPOX/FOLFIRI**/S1 plus oxaliplatin (SOX)/S1 plus irinotecan**
- The cytotoxic triplet FOLFOXIRI in selected fit and motivated patients where cytoreduction (tumour shrinkage) is the goal - and potentially also in fit patients with tumour *BRAF* mutations [II, B]
- Fluoropyrimidine monotherapy in patients unable to tolerate aggressive treatment [I, B].

18c. EGFR antibodies should be used in combination with:
- FOLFOX/FOLFIRI [I, A]
- Capecitabine-based and bolus 5-FU based regimens should not be combined with EGFR antibodies [I, E].

Recommendation 19 with revision: maintenance therapy

19a. Patients receiving **fluoropyrimidine** and oxaliplatin plus bevacizumab therapy as induction therapy, should be considered for maintenance therapy after **16–24 weeks**. The optimal maintenance treatment is a combination of a fluoropyrimidine (plus bevacizumab). bevacizumab as monotherapy is not recommended [I, B].

19b. Patients receiving FOLFIRI can continue on induction therapy—at a minimum—for as long as tumour shrinkage continues and the treatment is tolerable [V, B].

19c. For patients receiving initial therapy with FOLFOXIRI plus or minus bevacizumab, a fluoropyrimidine plus bevacizumab may be considered as maintenance therapy (as was done in the pivotal trials examining FOLFOXIRI [144, 145]).

19d. For patients receiving initial therapy with single-agent fluoropyrimidine (plus bevacizumab), induction therapy should be maintained [V, A].

19e. Individualisation **of treatment approaches based on** discussion with the patient is essential [V, A].

19f. Initial induction therapy or a second-line therapy has to be reintroduced at radiological or first signs of symptomatic progression. If a second-line therapy is chosen, re-introduction of the initial induction treatment should be a part of the entire treatment strategy [III, B].

Recommendation 20 with revision: second-line combinations with targeted agents

20a. Patients who are bevacizumab naïve should be considered for treatment with an antiangiogenic (bevacizumab or aflibercept) second-line [I, A]. The use of aflibercept should be restricted to combination with FOLFIRI for patients progressing on an oxaliplatin-containing regimen [I, A].

20b. Patients who received bevacizumab first-line should be considered for treatment with:
- Bevacizumab **beyond progression** strategy [I, A], or
- Aflibercept or ramucirumab (in combination with FOLFIRI) when treated in first line with oxaliplatin [I, A], or
- EGFR antibodies in combination with FOLFIRI/irinotecan for patients with *RAS* wt (*BRAF* wt) disease
  - Relative benefit of EGFR antibodies is similar in later lines compared with second-line [II, A].

20c. Patients who are fast progressors on first-line bevacizumab-containing regimens, should be considered for treatment with aflibercept or ramucirumab (only in combination with FOLFIRI) [II, B], and—in the case of patients with *RAS* wt disease and no pre-treatment with anti-EGFR therapy—EGFR antibody therapy, preferably in combination with chemotherapy [II, B].

Recommendation 21 with revision: Third-line therapy

21a. In *RAS* wt and *BRAF* wt patients not previously treated with EGFR antibodies cetuximab or panitumumab therapy should be considered
- Cetuximab and panitumumab are equally active as single agents [I, A]
- The combination of cetuximab with irinotecan is more active than cetuximab alone, in irinotecan refractory patients [II, B]
- There is no unequivocal evidence to administer the alternative anti-EGFR antibody, if a patient is refractory to one of the anti-EGFR antibodies [I, C].

21b. 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 country approvals** [I, B]
- Regorafenib is superior to placebo in terms of OS although there are toxicity concerns in frail patients.

21c. Trifluridine/tipiracil (FTD/TPI, TAS-102) 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 country approvals** [I, B].

Continued

Consensus recommendations on the use of cytotoxics and biologicals in the first- and subsequent-line treatment of patients with mCRC

Revised consensus recommendation A1 for patients where cytoreduction with 'conversion' and/or the integration of local ablative treatment is the goal

- A1a. For those patients who have **left-sided** *RAS* wt disease, a cytotoxic doublet plus an EGFR antibody should be the treatment of choice **and for those with right-sided *RAS* wt disease, a cytotoxic triplet plus bevacizumab should be, or a cytotoxic doublet plus an EGFR antibody can be, the treatment of choice.**
- A1b. For those patients with *RAS* mutant disease, a cytotoxic doublet plus bevacizumab or cytotoxic triplet plus bevacizumab **(in suitable patients)** are the preferred options.
- A1c. Patients should be revaluated for their disease status every 2 months in order to ensure that resectable patients are not overtreated.
- A1d. If, after the first re-evaluation at 2 months, there is evidence of tumour shrinkage patients should be recommended for either potentially curative surgery or the most suitable LAT strategy—with a view to eliminating all evidence of disease (i.e.: R0 resection, no evidence of disease).
- A1e. **If there is not a sufficient response after a maximum of 4 months** it is suggested that the cytotoxic doublet is changed in order to **retain** the chance of resection [178].
- A1f. Where there is evidence for cytoreduction but the patients are not suitable for surgery, they should continue on combination chemotherapy plus the appropriate biological dependent on *RAS* and *BRAF* mutation status as indicated in Figure 1.
- A1g. Where there is evidence of disease progression, patients should continue to second-line therapy (Figure 1).
- A1h. Toxicity might also require a change to an alternative regimen.

Revised consensus recommendation A2 for patients where cytoreduction is needed because of aggressive biology and/or risk of developing or existing severe symptoms

- A2a. For those patients who have **left-sided** *RAS* wt disease, a cytotoxic doublet plus an EGFR antibody **is the** preferred option, although a cytotoxic triplet plus or minus bevacizumab may be an alternative for selected, very fit and motivated patients **with left-sided *BRAF* mutant disease**. **For those with right-sided *RAS* wt disease, a cytotoxic triplet plus bevacizumab should be, or a cytotoxic doublet plus an EGFR antibody can be, the treatment of choice.**
- A2b. For those patients with *RAS* mutant disease, a cytotoxic doublet plus bevacizumab is the preferred option. A cytotoxic triplet plus or minus bevacizumab may be an alternative for selected, very fit and motivated patients.
- A2c. Patients should be revaluated for their disease status every 2 months.
- A2d. Treatment should not be changed in patients without tumour progression and not suffering from major toxicity.

Revised consensus recommendation B1 for patients where disease control is the goal

- B1a. For these patients, a cytotoxic doublet in combination with bevacizumab is recommended for **patients with *RAS* mutant or right-sided *RAS* wt disease**. In patients with **left-sided** *RAS* wt tumours a cytotoxic doublet plus an EGFR antibody **should be the treatment of choice**.
- B1b. Patients should be revaluated for their disease status every 2–3 months.
- B1c. In patients with a good response or at least disease control, active maintenance therapy should be considered. A fluoropyrimidine plus bevacizumab is the preferred option**, single-agent fluoropyrimidine is another option** if they started their treatment with a cytotoxic doublet plus bevacizumab.
- B1d. Where there is evidence of disease progression patients should continue to second-line therapy (Figure 1).
- B1e. Toxicity might also require a change to second-line therapy.

Singapore and Taiwan with an amendment to the text for recommendation 4f (Table 1), which changed the turnaround time for *RAS* testing from ≤7 days to ≤10 days for 90% of specimens. In China, Korea, Malaysia, Singapore and Taiwan the testing laboratories are accredited, the tests validated and regular audits are carried out. In Singapore the laboratories may be accredited to the equivalent of Laboratory MS ISO 15189 standards,

BRAF testing

ESMO recommendation 5 with revision: BRAF testing

5. Tumour *BRAF* mutation **(V600E)** status should be assessed alongside the assessment of tumour *RAS* mutational status for prognostic assessment (and/or potential selection for clinical trials) [A=83%, B=17% and I, B].

The Asian experts agreed either completely, or with some reservation, with the recommendation for *BRAF* testing (Table 1 and supplementary Table S2, available at *Annals of Oncology* online) accompanied by the modification indicated in bold text in Table 1 above. Tumour *BRAF* (V600E) mutations are a significant negative prognostic indicator for patients with mCRC [44–47], and are associated with a distinct pattern of metastatic spread [47]. Tumour *BRAF* mutations have also been shown to be prognostic in Asian patients [48]. Retrospective studies in Japanese patients with mCRC have revealed that a tumour *BRAF* V600E mutation is a poor prognostic indicator [49, 50], and that its prevalence appears to be slightly lower than among Caucasian patients (5.4%–6.7% versus 5%–12%) [51]. The data are somewhat conflicting as to whether tumour *BRAF* (V600E) mutations confer resistance to EGFR antibody therapy [52, 53]. A lack of response to EGFR antibody therapy has been reported in pretreated Japanese patients with *BRAF* V600E mutant mCRC [54]. The experts from Japan (revised JSMO Guidelines [2017] Japanese only) [55], China (CSCO guidelines) [18], Korea, Singapore and Taiwan fully agreed with the recommendation that tumour *BRAF* testing should be conducted alongside an assessment of tumour *RAS* mutational status. Malaysia could

only agree to the recommendation with some reservation due to questionable clinical utility.

Data from a post hoc analysis of 48 patients with *BRAF* mt mCRC from the FIRE-3 study were published almost simultaneously with the expert meeting in Kobe and showed a higher objective response rate (ORR) for patients receiving infusional 5-fluorouracil (5-FU), leucovorin and irinotecan (FOLFIRI) plus cetuximab than for those receiving FOLFIRI plus bevacizumab (ORR 52% versus 40%) [56]. More recently, data from the German, randomised, phase II, VOLFI trial comparing 5-FU, leucovorin, oxaliplatin and irinotecan (FOLFOXIRI) with FOLFOXIRI plus panitumumab (primary end point ORR) have been reported at the ESMO 2017 Annual Meeting in Madrid [57]. The addition of panitumumab to FOLFOXIRI increased the ORR compared with FOLFOXIRI alone and in patients with tumour *BRAF* (V600E) mutations the ORRs were 71.4% and 22%, for FOLFOXIRI plus panitumumab and FOLFOXIRI, respectively. Neither of these data sets were available at the time of the meeting in Kobe and were not discussed, but might need to be considered, going forward, as should emerging data from recent or ongoing clinical trials evaluating different combinations of MEK, BRAF, EGFR inhibition and/or chemotherapy [58–60].

Tumour MMR testing

ESMO recommendation 6 with revision: tumour mismatch repair (MMR) testing

6a. **Immunohistochemistry (IHC) tests for MMR proteins or PCR tests for microsatellite instability (MSI)** in the metastatic disease setting can assist clinicians in genetic counselling [A=100% and II, B].

6b. **Tumour MMR** testing has strong predictive value for the use of immune check-point inhibitors in the treatment of patients with mCRC [A=100% and II, B].

The frequency of DNA MMR deficiency in stage IV CRC is about 4–8% in Western countries [9], and about 1.9–3.7% in Japan [61, 62]. Since Asian experts view IHC and PCR as complementary techniques for evaluating tumour MMR deficiency, all the Asian experts agreed [A=100%] with the recommendations for tumour MMR testing accompanied by the modifications to 'recommendations 6a and b' indicated in bold text above. They also all agreed that tumour MMR testing has strong predictive value for the use of immune check-point inhibitors in the treatment of mCRC patients [63, 64].

Biomarkers of chemotherapy sensitivity and toxicity

ESMO recommendation 7 with revision: biomarkers of chemotherapy sensitivity and toxicity

7a. Dihydropyrimidine dehydrogenase (DPD) testing before 5-FU administration remains an option but is not routinely recommended [A=100% and II, D].

7b. UDP glucuronosyltransferase 1 family polypeptide A1 (UGT1A1) phenotyping remains an option and **is recommended to be 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* [A=100% and III, C] and including the * amendment below

> ***Depending on the prevalence of *UGT1A1* polymorphisms per country a lower irinotecan threshold dose for *UGT1A1* genotyping may be used.**

7c. Excision repair cross complementation group 1 (ERCC1) expression cannot be recommended for use as a biomarker for treatment decisions involving the use of oxaliplatin in routine clinical practice, but could be included prospectively in clinical trials [A=100% and III, D].

7d. Thymidylate synthase (TS) activity and TS enhancer region (*TSER*) genotyping are not recommended for use in clinical practice [A=100% and II, D].

The experts agreed with all four recommendations after discussion and the provision of some amended text with regard to UGT1A1 phenotyping, 'recommendation 7b'. The enzyme activity of UGT1A1 is closely associated with genetic polymorphisms of *UGT1A1*, especially *UGT1A1* *28 and *UGT1A1* *6. In Asian patients, the frequency of the *UGT1A1* *28 variant is much lower than that in Caucasian patients, whilst, the *UGT1A1* *6 variant is more common in Asian populations than in Western patient populations [65]. Approximately 10% of Japanese patients are either homozygous or simultaneously heterozygous for *UGT1A1* *6 or *28, which is associated with the severity of irinotecan-induced toxicities [66, 67]. Some Japanese studies [68, 69], have reported that *UGT1A1* *6 or *28 homozygous genotypes increase the incidence of severe neutropenia but not diarrhoea, and the association between *UGT1A1* *6/*6 homozygosity and severe neutropenia in Asian populations has been verified in a meta-analysis [70]. For patients who are homozygous for *UGT1A1* *6 or *28, or show simultaneous heterozygosity for both *UGT1A1* *6 and *28, irinotecan dose reduction is strongly recommended, and for patients with homozygous genotypes, the maximum-tolerated dose as a single agent is considered to be 150 mg/m^2 [69, 71]. Recently, the Japanese, phase II QUATTRO study showed that patients receiving FOLFOXIRI plus bevacizumab had a higher incidence of grade 4 neutropenia and febrile neutropenia, particularly during the first two cycles, especially in patients with single heterozygous *UGT1A1* polymorphisms compared with those who were wild-type (wt) for *UGT1A1* [72]. For patients without *UGT1A1* homozygous genotypes or simultaneously heterozygous *UGT1A1* *6 or *28 genotypes, the safety profile for irinotecan used at a dose of 180 mg/m^2 was reported to be acceptable [73]. The experts from all six Asian countries recommended *UGT1A1* genotyping for patients receiving a >180 mg/m^2 dose of irinotecan per administration (see 'recommendation 7b' above).

With regard to the other markers of chemotherapy sensitivity and toxicity, a Japanese study showed that patients with DPD deficiency experienced serious toxicity, including death, following 5-FU treatment [74]. However, as the incidence of DPD deficiency in healthy Japanese volunteers is extremely low (0.1%–0.7%) [75], and an optimal method of DPD testing has not yet been established, the Asian experts agreed that DPD testing remains an option but is not routinely recommended. There are

also Japanese [76–78] and Chinese [79] studies of the role of ERCC1 as a potential biomarker for the efficacy of oxaliplatin therapy, but the evidence level is not strong enough to change clinical practice. TS expression has also been examined in several Japanese studies [80–82], suggesting that TS might be both a prognostic indicator and a predictive marker of 5-FU efficacy. The TS gene promoter enhancer region (*TSER*) genotype is reported not to be a marker for tumour sensitivity to 5-FU based oral adjuvant chemotherapy in Japanese patients with CRC [83]. To date there are no validated data from large-scale trials, therefore, the Asian experts supported the existing ESMO 'recommendation 7d'.

Emerging biomarkers and technologies

ESMO recommendation 8: emerging biomarkers not recommended for routine patient management outside of a clinical trial setting

The Asian experts agreed completely [A=100%] with all aspects of ESMO 'recommendation 8' (Table 1 and supplementary Table S2, available at *Annals of Oncology* online). A lower proportion of Japanese patients have *PIK3CA* mutations compared with Western patients [22, 49, 84]. Also, in a Japanese study *PIK3CA* mutations failed to predict a response to EGFR antibody therapy [85], whilst in a Chinese study the correlation was not strong enough to allow it to be applied as a negative predictive marker for EGFR-antibody therapy [86]. In the case of PTEN, loss of expression (determined by IHC) was reported in 20%–40% of Japanese CRC patients [87, 88], with no significant association between PTEN expression and efficacy in patients with *KRAS* wt mCRC treated with EGFR antibody therapy [89]. There is insufficient evidence from small retrospective Japanese studies of amphiregulin, epiregulin and transforming growth factor-α as predictive biomarkers for EGFR antibody therapy [90–93], and of EGFR protein expression [94, 95] and *EGFR* amplification [96] as predictive biomarkers for EGFR antibody therapy, to change the current ESMO recommendation. Takegawa et al., have recently reported that a higher proportion of patients resistant to the EGFR antibody cetuximab exhibit *HER2* amplification in their circulating tumour DNA (ctDNA) than those who are not resistant to cetuximab [97]. Whilst, in another study Japanese patients with high HER2 mRNA receiving EGFR antibody therapy had a significantly shorter progression-free survival (PFS) compared with patients with low *HER2* expression (median PFS 4.1 versus 9.0 months, $P=0.032$) [98]. Despite this, the experts agreed that evaluation of *HER2* gene amplification or *HER2* activating mutations is not recommended outside of a clinical trial environment. Similarly, analysis of mRNA showed that Japanese patients with high MET expression, treated with EGFR antibody therapy, had significantly shorter overall survival times than those with low MET expression (median overall survival 9.8 versus 17.3 months, $P=0.038$) [98]. There is no clear evidence for HER3 overexpression and *HER3* mutations, mesenchymal–epidermal transition (MET)/*MET* alterations (overexpression or gene amplification) in the resistance to EGFR antibody therapies. Thus, the evaluation of HER3 and MET receptor overexpression is generally not recommended outside of the setting of a clinical trial. In addition, patients with high hepatocyte growth factor (HGF) expression have been reported to have a significantly shorter PFS than patients with low HGF expression for EGFR antibody treatment [92]. Minor Fc fragment of IgG receptor 2a (*FCGR2A*) polymorphisms were also discussed, the prevalence of which is known to be lower in the Japanese population than in the Caucasian population [99]. However, an international study, which included Japan, to investigate the association between *FCGR* polymorphisms and cetuximab efficacy in patients with chemorefractory mCRC showed no significant differences in median PFS for patients with *FCGR2A*-HH versus non-HH or *FCGR3A*-VV versus non-VV polymorphisms [100]. Therefore, the evaluation of *FCGR* polymorphisms cannot be recommended outside of the setting of a clinical trial.

ESMO recommendation 9: emerging technologies

The Asian experts agreed completely with all aspects of 'recommendation 9' [A=100%] (Table 1 and supplementary Table S2, available at *Annals of Oncology* online). Retrospective studies investigating the association between circulating tumour cell (CTC) levels and efficacy in Japanese patients have yielded inconsistent results [101, 102]. Thus, as per the ESMO recommendation, the utility of CTC assessments is not yet clear. A number of tumour–blood concordance studies are currently being conducted in Asian patients that will undoubtedly validate the clinical utility of these technologies for identifying more tumour mutations in the blood of patients [90, 103, 104]. In an analysis of 44 patients with CRC in Singapore, ctDNA detection correlated with clinical events [105]. ctDNA was detectable in preoperative but not post-operative plasma, and also in patients with recurrent CRC. ctDNA was also detected in 11 out of the 15 cases at or before clinical or radiological recurrence of CRC, indicating the potential for early detection of metastasis [105]. In addition, data from a patient with multiple primary cancers illustrated the specificity of the assay to distinguish between CRC recurrence and a second primary cancer [105]. However, the utility of all these techniques including microRNAs (miRNAs) [106, 107], have not yet been proven in clinical practice.

Local ablative treatment, including surgery, and management of patients with oligometastatic disease

ESMO recommendation 10: oligometastatic disease (OMD)

All the Asian experts agreed [A=100%] with the ESMO 'recommendations 10a and 10b' (Table 1 and supplementary Table S3, available at *Annals of Oncology* online).

ESMO recommendation 11: imaging in the identification and management of disease

All the Asian experts agreed [A=100%] with the ESMO 'recommendations 11a and 11b' (Table 1 and supplementary Table S3, available at *Annals of Oncology* online).

ESMO recommendation 12 with revision: perioperative treatment

12a. Both technical criteria for resection and prognostic considerations define the need for systemic perioperative therapy [A=100% and IV, B].

12b. In patients with clearly resectable disease and favourable prognostic criteria, perioperative treatment may not be necessary and upfront resection is justified [A=100% and I, C].

12c. In patients with technically resectable disease where the prognosis is unclear or probably unfavourable, perioperative combination chemotherapy (**a fluoropyrimidine plus oxaliplatin**) should be administered [A=66%, B=34% and I, B].

12d. Targeted agents should not be used in **patients with** resectable **metastases during perioperative therapy** [A=100% and II, E].

12e. In situations where the criteria for prognosis and resectability are not sharply defined, perioperative therapy should be considered (as part of a continuum of treatment option) [A=83%, B=17% and IV, B]. Patients with synchronous onset of metastases should be allocated to this group and therapeutic pathway.

12f. **In patients who have not received preoperative chemotherapy with favourable oncological and technical (surgical) criteria, there is no strong evidence to support the use of adjuvant chemotherapy [II, C], whereas patients with unfavourable criteria may benefit from treatment [III, B]. Postoperative treatment with a fluoropyrimidine plus oxaliplatin is recommended [IV, B]** [A=66%, B=34%].

12g. In patients who have not received any previous chemotherapy, adjuvant treatment with infusional 5-FU, leucovorin and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin [CAPOX (XELOX)] is recommended (unless patients were previously recently exposed to oxaliplatin-based adjuvant chemotherapy). This recommendation was incorporated in to the revised 'recommendation 12f' above recommendation and deleted from the Asian guidelines.

12h. Decision-making should include patients' characteristics and preferences [A=100% and IV, B].

There was considerable discussion about 'recommendations 12c, d and f', with a lack of total agreement between countries for the three statements going forward. ESMO 'recommendation 12d' was reworded, and 'recommendation 12g' was deleted and incorporated in to a reworded version of 'recommendation 12f'. In the Japanese JSCCR 2016 guidelines for the treatment of patients with CRC [7], the technical criteria for resection of liver or lung metastases are as follows: (i) the patient is capable of tolerating surgery, (ii) the primary tumour has been controlled or can be controlled, (iii) the metastatic liver or lung tumour(s) can be completely resected, (iv) there are no extrahepatic or extrapulmonary metastases or they can be completely resected and (v) the function of the remaining liver or lung will be adequate. A Japanese multi-centre study identified four poor prognostic indicators: (i) $\geq$5 hepatic tumours, (ii) hepatic tumours size $>$5 cm, (iii) nodal status (N2) of primary cancer, and (iv) the presence of extrahepatic metastases [108], which was validated in another study with 1185 cases [109]. In Japan, upfront resection without perioperative chemotherapy for resectable liver metastases is regarded as standard therapy, because there is no evidence for perioperative treatment prolonging overall survival. The 5-year survival rate for Japanese patients undergoing hepatic resection without perioperative chemotherapy in a multi-institutional study was 33–38% [110, 111], which is consistent with those reported in Western studies (28–37%) [112, 113]. However, a randomised controlled phase III Japanese study is being conducted to demonstrate the feasibility and efficacy of adjuvant chemotherapy with 12 cycles of modified FOLFOX6 (m FOLFOX6) compared with hepatectomy alone in patients with curatively resected colorectal liver metastases [114]. EGFR monoclonal antibodies are not to be used for the preoperative treatment of patients with resectable colorectal liver metastases in Japan outside of a clinical trial, based on the data from the New EPOC clinical trial [115]. There are no data for bevacizumab as perioperative therapy for patients with resectable liver metastases in Asia, although protection from hepatic sinusoidal injury has been reported in patients receiving a bevacizumab-containing regimen [116]. A phase III trial evaluated the efficacy of adjuvant chemotherapy with uracil-tegafur plus leucovorin (UFT/LV) for unselected patients undergoing curative hepatic resection for colorectal liver metastases [117]. In the subgroup of patients with multiple metastasis, the recurrence-free survival was higher in the UFT/LV group than in the surgery alone group (P=0.019), suggesting that patients with unfavourable criteria may benefit from adjuvant treatment. Furthermore, although Singapore has adopted the ESMO guidelines in the Singapore Cancer Network (SCAN) Guidelines for Systemic Therapy of CRC [25] with regard to all other statements under ESMO 'recommendation 12', the experts from Singapore suggested that 'recommendation 12d' above be reworded to 'Targeted agents should not be used in patients with resectable metastases during perioperative therapy'. In Taiwan, biologics/targeted agents could be accepted for preoperative treatment in patients with mCRC regardless of their resectability. After curative resection of metastatic lesions (and primary lesions), targeted agents are not included as a component of adjuvant or post-operative therapy in Taiwan.

ESMO recommendation 13: conversion therapy

All the Asian experts agreed [A=100%] with ESMO 'recommendations 13a, b and c' (Table 1 and supplementary Table S3, available at *Annals of Oncology* online). Treatment intensification resulted in an increased response rate, a consequential increase in R0 resection rate and improved survival in a prospective, randomised, phase II trial conducted in 138 Chinese patients with *KRAS* exon 2 wt liver-limited mCRC [118]. The addition of the EGFR antibody cetuximab to chemotherapy (FOLFIRI/mFOLFOX6) led to a statistically significant increase in R0 resection rate (25.7% in the cetuximab arm versus 7.4% in the chemotherapy alone arm). Early tumour shrinkage, defined as a $\geq$20% reduction in the longest diameters of the target lesions compared with baseline at the first evaluation (8 weeks), was shown to be an independent predictor of improved overall survival (HR 0.56, P=0.007). In Japan, successful conversion therapy tends to be

associated with higher response rates, and survival in patients achieving conversion is significantly higher than that in patients with unresected liver metastases (median overall survival 40.5 versus 24.3 months, P=0.034) [119]. However, the resectability may be biased by various other factors [120].

ESMO recommendation 14: ablative techniques

All the Asian experts agreed [A=100%] with the ESMO 'recommendation 14' (Table 1 and supplementary Table S3, available at *Annals of Oncology* online).

ESMO recommendation 15: local ablation techniques

15a. In patients with unresectable liver metastases only, or OMD, local ablation techniques such as thermal ablation or high conformal radiation techniques (e.g. stereotactic body radiation [SBRT], high dose rate [HDR]-brachytherapy) can be considered. The decision should be taken by a multidisciplinary team (MDT) based on local experience, tumour characteristics, and patient preference [A=83, B=17% and IV, B].

15b. In patients with lung only or OMD of the lung, ablative high conformal radiation or thermal ablation may be considered if resection is limited by comorbidity, the extent of lung parenchyma resection, or other factors [A=83%, B=17% and IV, B].

15c. SBRT is a safe and feasible alternative treatment of oligometastatic colorectal liver and lung metastases in patients not amenable to surgery or other ablative treatments [A=83%, B=17% and IV, B].

15d. Radiofrequency ablation (RFA) can be used in addition to surgery with the goal of eradicating all visible metastatic sites [A=83%, B=17% and II, B].

All the Asian experts accepted ESMO 'recommendations 15a-d', either completely or with some reservation (supplementary Table S3, available at *Annals of Oncology* online). In a small retrospective analysis of 102 Japanese patients with unresectable metastatic liver lesions, thermal ablation in addition to hepatectomy achieved a local tumour control rate of 95% [121]. Also, Inoue et al. [122], reported that multi-modality therapy (including radiofrequency thermal ablation and radiotherapy) for patients with lung metastases from CRC could achieve a median overall survival of 38.6 months and a 3-year survival rate of 87.5%. Thermal ablation techniques have also proved to be efficacious in the ablation of CRC lung metastases, achieving high local control rates [123]. Other retrospective studies have reported high efficacy for surgery combined with RFA [124] and confirmed its safety after chemotherapy in patients with CRC [125]. Several small retrospective Asian studies have demonstrated relatively good local control with SBRT, with local control rates ranging from 53% to 100%, and 2-year overall survival ranging from 47% to 84.3% in patients with unresectable pulmonary or hepatic metastases [121, 126–132]. It should be noted that some of these techniques are not available in some Asian countries.

ESMO recommendation 16 with revision: embolisation

16a. For patients with liver-limited disease failing the available chemotherapeutic options

- Radioembolisation with yttrium-90 microspheres **can** be considered [A=100% and II, **C**]
- Chemoembolisation may be also considered as a treatment option [A=100% and IV, B].

16b. Radioembolisation (and chemoembolisation) of colorectal liver metastases in earlier treatment lines may be interesting as 'consolidation treatment' but should be limited to clinical trials. [A=100%].

All the Asian experts agreed [A=100%] .with ESMO 'recommendations 16a and b' (Table 1 and supplementary Table S3, available at *Annals of Oncology* online), although the wording and level of evidence for 'recommendation 16a' were revised. For the original statement, which included the word **should** instead of **can** the level of agreement was A=0%; B=67%, C=33%. To date, there is no report of the use of Yttrium-90 microspheres for the treatment of colorectal liver metastases in Asian patients, and there is no established evidence of the efficacy of chemoembolisation compared with systemic chemotherapy for the treatment of colorectal liver metastases, although a single-arm phase I/II study of transcatheter arterial chemoembolisation using cisplatin with degradable starch microspheres (DSMs) showed an antitumour effect on colorectal liver metastases after the failure of FOLFOX therapy [133]. The response and disease control rates for the liver metastases were 61.1% and 92.4%, respectively. A prospective multicentre study of RFA combined with hepatic arterial chemoembolisation using DSMs mixed with mitomycin C also demonstrated promising anticancer effects on colorectal liver metastases [134]. The 2-year local tumour control rates were 92.0%. In addition, Japanese studies suggest that hepatic arterial infusion (HAI) has antitumour activity and is well tolerated [135, 136]. The Japanese JSCCR guidelines [7] do not recommend HAI with or without systemic chemotherapy for the treatment of colorectal liver metastases as an alternative to standard systemic chemotherapy, because the data are insufficient to support such an approach. There are essentially no other Asian data on chemoembolisation except for a Taiwanese study [137]. Again, it should be noted that some of these techniques are not available in some Asian countries.

ESMO recommendation 17 with revision: cytoreductive surgery and HIPEC

17. Complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) can be considered for patients with limited peritoneal metastases in centres which are experienced in the use of HIPEC [A=100% and III, **C**].

All the Asian experts agreed with ESMO 'recommendation 17' following the deletion of the word 'very' from before 'experienced' and the revision of the level of evidence and grade of recommendation from II, B to III, C'. Complete cytoreductive surgery combined with HIPEC is not commonly used in Asia.

A retrospective, single institution study conducted in Japan has reported the median survival time and 5-year overall survival rates in 142 patients treated with cytoreductive surgery and HIPEC to be 24.4 months and 23%, respectively. The median survival times and 5-year overall survival rates were 25.9 months and 20% in patients with no residual visible tumour nodules compared with 8.0 months and 10% in patients with residual tumour nodules ($P<0.001$) [138].

Treatment of metastatic disease

ESMO recommendation 18 with revision: first-line systemic therapy combinations according to targeted agent used

18a. Biologicals (targeted agents) are indicated in the first-line treatment of most patients unless contraindicated [A=100% and I, A].

18b. **When used**, the VEGF antibody bevacizumab should be **administered** in combination with:

- The cytotoxic doublets FOLFOX/CAPOX/FOLFIRI/**S-1 plus oxaliplatin (SOX)/S1 plus irinotecan** [A=100% and 1, A].
- The cytotoxic triplet FOLFOXIRI in selected fit and motivated patients where cytoreduction (tumour shrinkage) is the goal—and potentially also in fit patients with tumour *BRAF* mutations [A=100% and II, B].
- Fluoropyrimidine monotherapy in patients unable to tolerate aggressive treatment [A=100% and I, B].

18c. EGFR antibodies should be used in patients with *RAS* wt disease in combination with:

- FOLFOX/FOLFIRI [A=100% and I, A].
- Capecitabine-based and bolus 5-FU based regimens should not be combined with EGFR antibodies [A=100% and I, E].

All the Asian experts agreed [A=100%] with ESMO *recommendation 18* (Table 1 and supplementary Table S4, available at *Annals of Oncology* online) following an amendment to 'recommendation 18b' to include the regimens SOX and S-1 plus irinotecan as potential combination partners for bevacizumab [7, 139]. The randomised phase III TRICOLORE trial investigating the non-inferiority of the combination therapy regimen S-1, irinotecan and bevacizumab (administered as either a 3- or 4-week regimen) to either mFOLFOX6 or CAPOX plus bevacizumab has just recently reported S-1, irinotecan and bevacizumab to be non-inferior to mFOLFOX6 or CAPOX plus bevacizumab in the first-line therapy of mCRC [140, 141]. With regard to recommendation 18a, which was not modified by the Asian experts, there is no unequivocal evidence that one class of biologic (EGFR antibody versus antiangiogenic [bevacizumab]) is better in combination with chemotherapy in patients with *RAS* wt mCRC. The Western FIRE-3 and PEAK studies [35, 36, 142] have demonstrated a benefit in overall survival for EGFR antibody therapy, compared with bevacizumab therapy, as an adjunct to combination chemotherapy in the first-line treatment of patients with *RAS* wt mCRC, but it is unclear whether this observation applies to Japanese or other Asian patients as no, or only a few, patients of Asian ethnicity were included in these studies. However, EGFR antibody therapy in combination with either FOLFOX or FOLFIRI is one of the recommended treatment options for Japanese patients in the Japanese JSCCR guidelines [7], and other Asian patients, with *RAS* wt mCRC. The ongoing phase III PARADIGM study comparing FOLFOX plus panitumumab with FOLFOX plus bevacizumab in Japanese patients with *RAS* wt mCRC will hopefully clarify the situation for Asian patients [143]. Recent data [11] on the location of the primary tumour in patients with *RAS* wt will also impact on this decision going forward (see later in this document).

ESMO recommendation 19 with revision: maintenance therapy

19a. Patients receiving **fluoropyrimidine** plus oxaliplatin plus bevacizumab therapy as induction therapy, should be considered for maintenance therapy after **16–24 weeks**. The optimal maintenance treatment is a combination of a fluoropyrimidine (plus bevacizumab). Bevacizumab as monotherapy is not recommended [A=83%, B=17% and I, B].

19b. Patients receiving FOLFIRI can continue on induction therapy—at a minimum—for as long as tumour shrinkage continues and the treatment is tolerable [A=100% and V, B].

19c. For patients receiving initial therapy with FOLFOXIRI plus or minus bevacizumab, a fluoropyrimidine plus bevacizumab may be considered as maintenance therapy (as was done in the pivotal trials examining FOLFOXIRI [144, 145]) [A=83%, B=17%].

19d. For patients receiving initial therapy with single-agent fluoropyrimidine (plus bevacizumab), induction therapy should be maintained [A=100% and V, A].

19e. Individualisation **of treatment approaches based on** discussion with the patient is essential [A=100% and V, A].

19f. Initial induction therapy or a second-line therapy has to be reintroduced at radiological or first signs of symptomatic progression. If re-treatment is chosen, re-introduction of the initial induction treatment should be a part of the entire treatment strategy [A=100% and III, B].

The Asian experts essentially agreed with 'recommendation 19' following an amendment to 'recommendation 19a' to 'fluoropyrimidine plus oxaliplatin' to allow for inclusion of S-1 in combination with oxaliplatin for Asian patients, the placing of a bracket around bevacizumab because fluoropyrimidine monotherapy is used as maintenance therapy in China and other Asian countries [146], and the replacement of time in weeks rather than cycles for the timing of any decision about a switch to maintenance therapy. 'Recommendation 19e' was also slightly reworded for the sake of clarification. Two prospective Japanese studies of maintenance therapy of eight cycles of a FOLFOX-based regimen followed by maintenance therapy with a fluoropyrimidine plus bevacizumab, showed a median PFS of 11.8–12.8 months [147, 148]. However, discontinuation strategies are not popular

in Japan. In general, when patients have grade ≥2 peripheral sensory neuropathy their oxaliplatin-based therapy is stopped and their treatment deescalated to fluoropyrimidine plus bevacizumab maintenance therapy. Thus, the planned introduction of maintenance therapy 'may' be considered after six 3-weekly cycles of CAPOX or SOX or eight 2-weekly cycles of FOLFOX. There is a paucity of Asian studies supporting the use of bevacizumab as monotherapy, and bevacizumab as monotherapy is not recommended. Maintenance therapy should be continued until progression. The use of FOLFOXIRI plus bevacizumab as initial therapy was queried by the experts from Malaysia.

ESMO recommendation 20 with revision: second-line combinations with targeted agents

20a. Patients who are bevacizumab naïve should be considered for treatment with an antiangiogenic (bevacizumab or aflibercept) second-line [A=100% and I, A]. The use of aflibercept should be restricted to combination with FOLFIRI for patients progressing on an oxaliplatin-containing regimen [A=100% and I, A].

20b. Patients who received bevacizumab first line should be considered for treatment with:

- Bevacizumab **beyond progression** strategy [A=100% and I, A], or
- Aflibercept or ramucirumab (in combination with FOLFIRI) when treated in first line with oxaliplatin [A=100% and I, A], or
- EGFR antibodies in combination with FOLFIRI/irinotecan for patients with *RAS* wt *(BRAF* wt) disease
  - Relative benefit of EGFR antibodies is similar in later lines compared with second-line [A=100% and II, A].

20c. Patients who are 'fast progressors' on first-line bevacizumab-containing regimens, should be considered for treatment with aflibercept or ramucirumab (only in combination with FOLFIRI) [II, B], and—in the case of patients with *RAS* wt disease and no pre-treatment with anti-EGFR therapy—EGFR antibody therapy, preferably in combination with chemotherapy [A=100% and II, B].

All the Asian experts agreed [A=100%] with 'recommendations 20a–c' (Table 1 and supplementary Table S4, available at *Annals of Oncology* online). This total agreement was supported not only by evidence from Western trials but also supported by evidence from Asian studies. Several phase II studies in Japan and China have demonstrated the efficacy and safety of bevacizumab in patients who have received first-line 5-FU-based or oxaliplatin-based first-line chemotherapy without bevacizumab with comparable efficacy results to the Western studies [73, 149, 150]. In addition, several phase II studies in Japan, China and Korea have demonstrated the efficacy and safety of bevacizumab beyond progression in patients who have received first-line therapy including bevacizumab with comparable overall survival results to the Western studies [151–158]. A multi-national (Japan, China, South Korea), randomised, non-inferiority, phase III trial of second-line chemotherapy for patients with mCRC, comparing the efficacy and safety of capecitabine plus irinotecan (XELIRI) with or without bevacizumab versus FOLFIRI with or without bevacizumab (the Asian XELIRI ProjecT (AXEPT) is ongoing [159], and the primary survival analysis will be presented at ESMO Asia 2017. The addition of ramucirumab to FOLFIRI after first-line treatment with oxaliplatin, fluoropyrimidine and bevacizumab has been shown to confer an overall survival benefit in a multi-centre, randomised, phase III trial of patients with mCRC that included Japan [160]. A Japanese phase Ib study confirmed that ramucirumab was well tolerated in patients with mCRC [161]. Whilst, a phase I dose-escalation study determined 4 mg/kg aflibercept to be the optimal dose in combination with FOLFIRI [162]. A phase II study in Japanese patients [163] has recently shown aflibercept to achieve an ORR, median PFS and median overall survival of 8.3%, 5.4 and 15.6 months, respectively. These efficacy and safety data were consistent with those reported for the VELOUR study [164], and support the use of aflibercept in combination with FOLFIRI for Asian patients progressing on an oxaliplatin-containing regimen.

ESMO recommendation 21 with revision: third-line therapy

21a. In *RAS* wt and *BRAF* wt patients not previously treated with EGFR antibodies cetuximab or panitumumab therapy should be considered

- Cetuximab and panitumumab are equally active as single agents [A=100% and I, A]
- The combination of cetuximab with irinotecan is more active than cetuximab alone, in irinotecan refractory patients [A=100% and II, B]
- There is no unequivocal evidence to administer the alternative anti-EGFR antibody, if a patient is refractory to one of the anti-EGFR antibodies [A=100% and I, C].

21b. 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 country approvals** [A=100% and I, B]

- Regorafenib is superior to placebo in terms of overall survival although there are toxicity concerns in frail patients.

21c. Trifluridine/tipiracil (FTD/TPI, TAS-102) 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 country approvals** [A=100% and I, B].

All the Asian experts agreed with 'recommendations 21a–c', subject to the modifications made to 'recommendations 21b and c'. In the third-line setting, for patients with *RAS* wt/*BRAF* wt disease not previously treated with EGFR antibodies, previous studies have indicated that EGFR antibody therapy is more active than either FTD/TPI or regorafenib. Retrospective studies have reported the efficacy of EGFR antibodies third line for mCRC patients with *KRAS* wt disease [94, 165] with a randomised phase II trial, showing the non-inferiority of panitumumab compared

with cetuximab in combination with irinotecan [166]. The ASPECCT trial, which included patients from South Korea, China and India also showed that panitumumab was non-inferior to cetuximab for overall survival in patients with chemotherapy-refractory, *KRAS* wt mCRC [167]. A post hoc analysis [168], was conducted, in patients with refractory mCRC, to assess the efficacy and safety of regorafenib in the Japanese and non-Japanese patient populations of the CORRECT trial [169]. In Japanese patients, the median overall survival as well as the median PFS consistently favoured the patients receiving regorafenib over those receiving placebo (HR 0.81 and 0.47, respectively). However, certain regorafenib-associated toxicities were observed more frequently in Japanese patients than in non-Japanese patients, but were generally manageable [168]. In the Japanese post-marketing surveillance study of regorafenib treatment, performance status (PS) was related to PFS (median PFS, PS 0=9.1 months, PS 1=5.8 months, PS ≥2=3.4 months), therefore patients with a PS ≥2 might not be candidates for regorafenib therapy [170]. A randomised, placebo-controlled, Asian phase III study (the CONCUR trial) showed a survival benefit for regorafenib compared with placebo (HR 0.55) [171].

Also, a randomised, placebo-controlled phase II Japanese trial to investigate the efficacy and safety of FTD/TPI, reported a median overall survival of 9.0 months in the FTD/TPI group and 6.6 months in the placebo group (HR 0.56, $P = 0.0011$) [172]. The international, double-blind, phase III RECOURSE trial to assess the efficacy and safety of FTD/TPI in refractory mCRC patients (including Japanese patients) reported an overall survival of 5.3 months for placebo and 7.1 months for FTD/TPI (HR 0.68, $P<0.001$) [173]. A post hoc analysis of the RECOURSE trial showed both the overall survival and PFS benefits of FTD/TPI to be observed in each geographic subset of patients, with an acceptable safety profile [174]. Mayer et al. reported that the overall survival benefit of FTD/TPI was maintained irrespective of prior regorafenib use (HR 0.69) [173]. The TERRA trial also showed a significant prolongation of overall survival (HR 0.79) in East-Asian patients [175]. However, a note of caution was introduced by the experts from Singapore in relation to regorafenib dosing suggesting that some physicians may start with a lower dose e.g. 120 mg/day rather than 160 mg/day, with frequent dose monitoring for toxicity recommended. Post marketing surveillance of FTD/TPI showed the acceptable tolerability of this treatment in Japanese patients [176]. A phase I/II Japanese study to evaluate the efficacy and safety of FTD/TPI in combination with bevacizumab in patients with mCRC refractory to standard therapies reported a median PFS and disease control rate (DCR) by central assessment of 3.7 months and 64.0%, respectively [177].

Consensus recommendations on the use of cytotoxics and biologicals in the first- and subsequent-line treatment of patients with mCRC

The Asian experts initially voted for the ESMO 2016 consensus guidelines recommendations below without consideration of primary tumour location.

ESMO recommendation A1 with revision: consensus recommendation for patients where cytoreduction with 'conversion' and/or the integration of local ablative treatment is the goal

A1a. For those patients who have *RAS* wt disease, a cytotoxic doublet plus an EGFR antibody should be the treatment of choice [A=83% B=17%].

A1b. For those patients with *RAS* mutant disease, a cytotoxic doublet plus bevacizumab or cytotoxic triplet plus bevacizumab **(in suitable patients)** are the preferred options [A=66%, B=34%].

A1c. Patients should be revaluated for their disease status every 2 months in order to ensure that resectable patients are not overtreated [A=83%, B=17%].

A1d. If, after the first re-evaluation at 2 months, there is evidence of tumour shrinkage patients should be recommended for either potentially curative surgery or the most suitable local ablative treatment (LAT) strategy, with a view to eliminating all evidence of disease (i.e. R0 resection, no evidence of disease) [A=83%, B=17%].

A1e. **If there is not a sufficient response after a maximum of 4 months**, it is suggested that the cytotoxic doublet is changed in order to **retain** the chance of resection [178] [A=49%, B=51%].

A1f. Where there is evidence for cytoreduction but the patients are not suitable for surgery, they should continue on combination chemotherapy plus the appropriate biological dependent on *RAS* and *BRAF* mutation status as indicated in Figure 1 [A=100%].

A1g. Where there is evidence of disease progression, patients should continue to second-line therapy (Figure 1) [A=100%].

A1h. Toxicity might also require a change to an alternative regimen [A=100%].

ESMO recommendation A2: consensus recommendation for patients where cytoreduction is needed because of aggressive biology and/or risk of developing or existing severe symptoms

A2a. For those patients who have *RAS* wt disease, a cytotoxic doublet plus an EGFR antibody is the preferred option, although a cytotoxic doublet plus bevacizumab is a valid alternative. A cytotoxic triplet plus or minus bevacizumab may be an alternative for selected, very fit and motivated patients [A=100%].

A2b. For those patients with *RAS* mutant disease, a cytotoxic doublet plus bevacizumab is the preferred option. A cytotoxic triplet plus or minus bevacizumab may be an alternative for selected, very fit and motivated patients [A=100%].

A2c. Patients should be revaluated for their disease status every 2 months [A=100%].

A2d. Treatment should not be changed in patients without tumour progression and not suffering from major toxicity [A=100%].

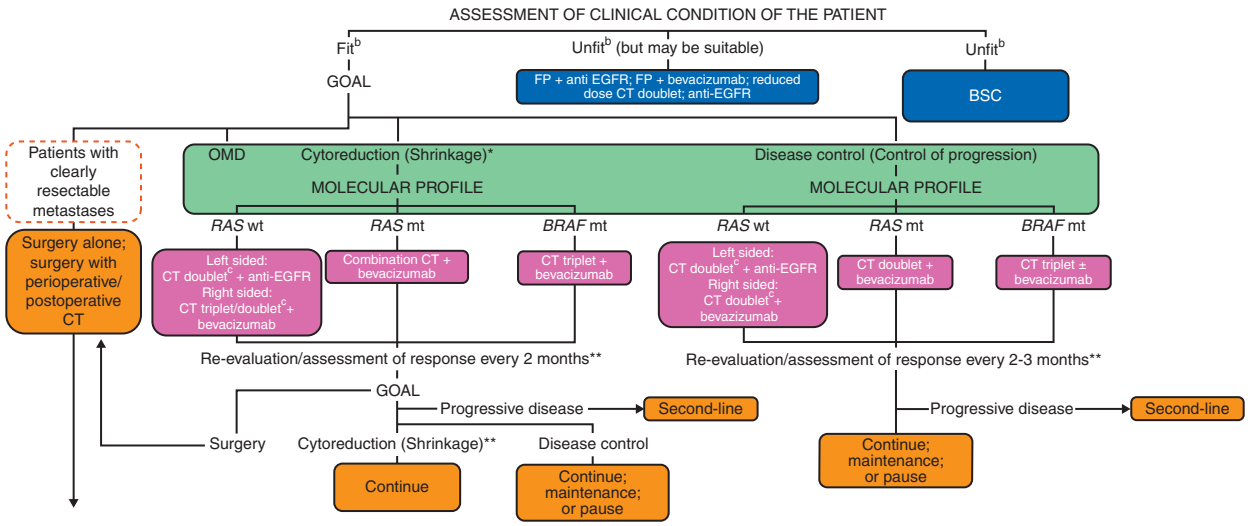

Figure 1. ESMO consensus guidelines treatment algorithm [9] adapted for Asian patients.[a] BSC, best supportive care; CT, chemotherapy; EGFR, epidermal growth factor receptor; FP, fluoropyrimidine; mt, mutant; NED, no evidence of disease; OMD, oligometastatic disease; wt, wild-type. [a]Cross references to Table 2; [b]Patients assessed as fit or unfit according to medical condition not due to malignant disease; [c]CT doublet, SOX (S-1 plus oxaliplatin) is an alternative to FOLFOX (infusional 5-fluorouracil, leucovorin and oxaliplatin) or, CAPOX (capecitabine plus oxaliplatin), and S-1 plus irinotecan is an alternative to FOLFIRI (infusional 5-fluorouracil, leucovorin and irinotecan). *Includes two subgroups: (1) those for whom intensive treatment is appropriate with the goal of cytoreduction (tumour shrinkage) and conversion to resectable disease; (2) those who need an intensive treatment, although they will never make it to resection or LAT, since they need a rapid reduction of tumour burden because of impending clinical threat, impending organ dysfunction, severe symptoms. **After two re-evaluations, consider maintenance.

ESMO recommendation B1 with revision: consensus recommendations for patients where disease control is the goal

B1a. For these patients, a cytotoxic doublet in combination with bevacizumab is recommended. In patients with *RAS* wt tumours a cytotoxic doublet plus an EGFR antibody is an alternative option [A=100%].

B1b. Patients should be revaluated for their disease status every 2–3 months [A=100%].

B1c. In patients with a good response or at least disease control, active maintenance therapy should be considered. A fluoropyrimidine plus bevacizumab is the preferred option **and single-agent fluoropyrimidine another option,** if they started their treatment with a cytotoxic doublet plus bevacizumab [A=100%].

B1d. Where there is evidence of disease progression patients should continue to second-line therapy (Figure 1) [A=100%].

B1e. Toxicity might also require a change to second-line therapy [A=100%].

Impact of primary tumour location on treatment choice

Since the publication of the recent ESMO consensus guidelines [9], an ESMO special article reporting the results of a retrospective pooled analysis of six trials (CRYSTAL [37], FIRE-3 [142], CALGB 80405 [179], PRIME [180], PEAK [35] in first line and 20050181 in second line [33]) on the prognostic and predictive value of primary tumour location (left- versus right-sided) for the treatment of patients with *RAS* wt mCRC with chemotherapy and EGFR antibody therapy, has been published [11]. *RAS* mutant tumour status is known to be a strong negative predictor for the efficacy of EGFR antibody therapy [27, 29, 30, 38, 39, 181]. In the pooled analysis [11], primary tumour location and tumour *RAS* wt mutation status were available for 2159 patients across the six randomised trials investigating a standard chemotherapy regimen in combination with EGFR antibody therapy (cetuximab or panitumumab) versus standard chemotherapy alone or in combination with bevacizumab. The individual trial data for the six trials showed patients with left-sided tumours receiving chemotherapy plus EGFR antibody therapy to have superior treatment outcomes in terms of overall survival, PFS and response rate, to patients with right-sided tumours receiving the same therapy. The predictive effect of primary tumour location for chemotherapy plus EGFR antibody therapy compared with chemotherapy alone, or chemotherapy plus bevacizumab, also differed significantly for patients with *RAS* wt tumours. A significant benefit ($P<0.001$) for chemotherapy plus EGFR antibody therapy was observed in patients with left-sided tumours for overall survival and PFS compared with no benefit ($P=0.381$ and $P=0.365$ for overall survival and PFS, respectively) in patients with right-sided tumours. Patients in both the large FIRE-3 and CALGB 80405 first-line trials, with left-sided *RAS* wt tumours, receiving chemotherapy plus EGFR antibody therapy (cetuximab), had significantly better treatment outcomes in terms of overall survival, PFS and response rate, than those receiving chemotherapy plus Bev. Limited, if any, benefit was observed from the addition of EGFR antibody therapy to chemotherapy in the treatment of patients with right-sided tumours,

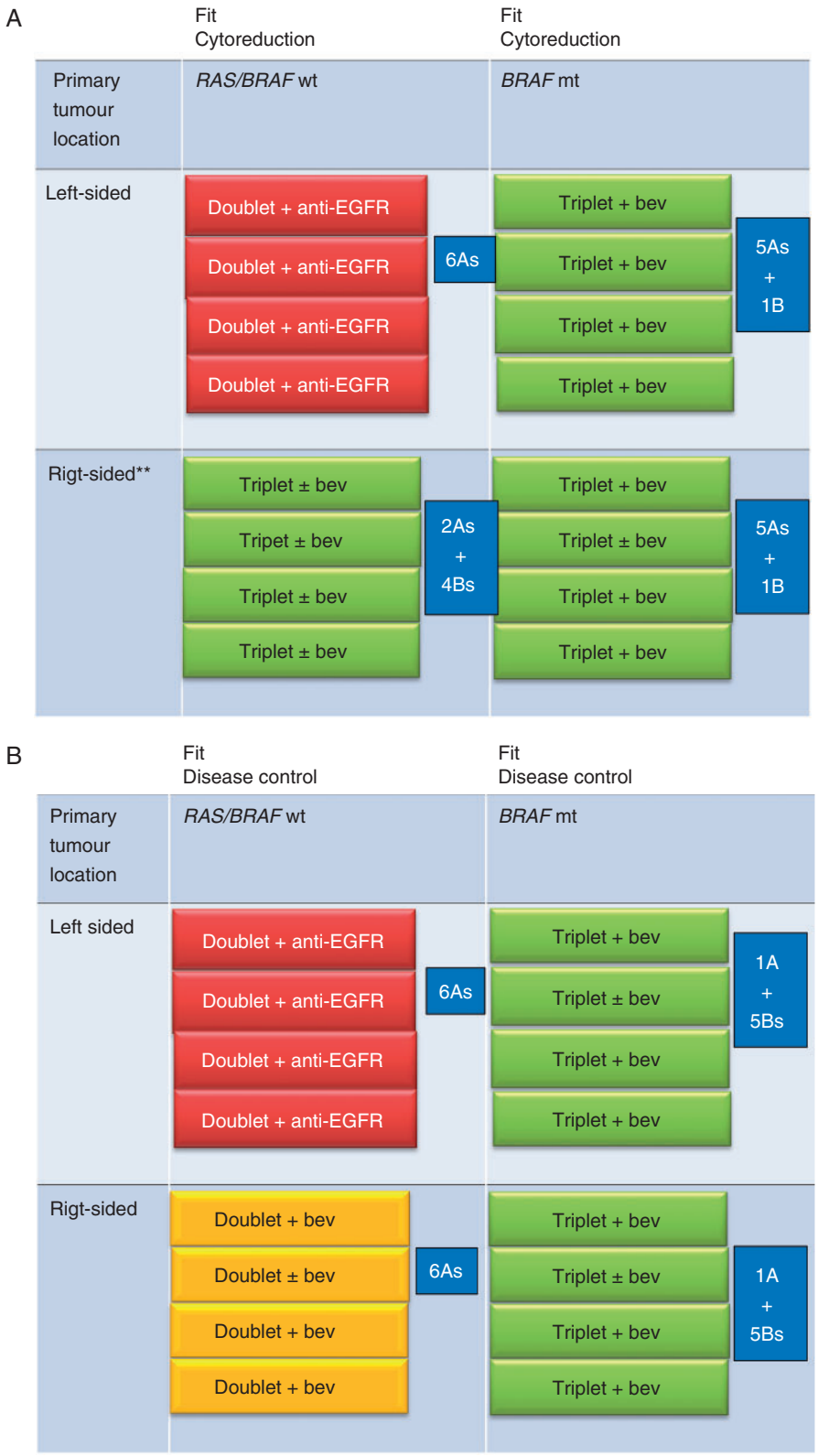

Figure 2. Results of voting on optimal treatment choices according to location of the primary tumour by ESMO experts*. (a) Cytoreduction; (b) disease control. *The ESMO expert recommendations from the meeting provided by the four ESMO experts (AC, FC, JYD, JT) with the voting on the level of agreement for each of the six Asian countries indicated in the blue boxes where A=agree (accept) completely and B =accept with some reservation; **second choice should be a chemotherapy doublet plus EGFR antibody therapy. A triplet ± bev regimen is contemplated for selected, fit patients only. Bev, bevacizumab; EGFR, epidermal growth factor receptor; mt, mutant; wt, wild-type.

Table 2. Systemic therapy choices adapted from ESMO consensus guidelines [9] for Asian patients with unresectable metastatic disease (excluding those with OMD) but including consideration of left- versus right-sided primary tumour location[a]

Category	Fit patients[b]						Unfit[b]	
Treatment goal	Cytoreduction (tumour shrinkage)			Disease control (control of progression)			May be unfit Palliation	Unfit
Molecular profile	*RAS* wt	*RAS* mt	*BRAF* mt	*RAS* wt	*RAS* mt	*BRAF* mt	Any	Any
First line								
Preferred choice								
Left-sided primary	CT doublet[c] + EGFR antibody[d,e]	CT doublet[c] + bevacizumab	FOLFOXIRI + bevacizumab	CT doublet[c] + EGFR antibody[d]	CT doublet[c] + bevacizumab	FOLFOXIRI ± bevacizumab	FP + EGFR antibody	BSC
Right-sided primary	FOLFOXIRI + bevacizumab	CT doublet[c] + bevacizumab	FOLFOXIRI + bevacizumab	CT doublet[c] + bevacizumab	CT doublet[c] + bevacizumab	FOLFOXIRI ± bevacizumab	FP + bevacizumab	
Second choice	CT doublet[c] + bevacizumab	FOLFOXIRI + bevacizumab	CT doublet[c] + bevacizumab	FP + bevacizumab		CT doublet[c] + bevacizumab	Reduced-dose CT doublet[c]	–
Third choice		FOLFOXIRI	FOLFOXIRI				If *RAS* wt may consider EGFR antibody therapy	–
Maintenance								
Preferred choice	FP + bevacizumab[f]	FP + bevacizumab	FP + bevacizumab	FP + bevacizumab[f]	FP + bevacizumab	FP + bevacizumab	FP + bevacizumab	–
Second choice	Pause	Pause	Pause	Pause	Pause	Pause	FP	–
Second-line								
Preferred choice	CT doublet[c] + bevacizumab	CT doublet[c] + bevacizumab	CT doublet[c] + bevacizumab	CT doublet[c] + bevacizumab or CT doublet[c] + EGFR antibody[d]	CT doublet[c] + bevacizumab	CT doublet[c] + bevacizumab		–
Second choice	CT doublet[c] + EGFR antibody[d,g] or FOLFIRI + aflibercept/ ramucirumab	FOLFIRI + aflibercept/ ramucirumab	FOLFIRI + aflibercept/ ramucirumab	FOLFIRI + aflibercept/ ramucirumab	FOLFIRI + aflibercept/ ramucirumab	FOLFIRI + aflibercept/ ramucirumab		–
Third line								
Preferred choice	CT doublet[c] + EGFR antibody[d,g] or irinotecan + cetuximab[g]	Regorafenib or FTD/TPI	Regorafenib or FTD/TPI	CT doublet[c] + EGFR antibody[d] or irinotecan + cetuximab[g]	Regorafenib or FTD/TPI	Regorafenib or FTD/TPI		–
Second choice	EGFR antibody monotherapy[g]			EGFR antibody monotherapy[g]				–
Third choice	Regorafenib or FTD/TPI			Regorafenib or FTD/TPI				–

[a]Cross references to Figure 1.

[b]Patients assessed as fit or unfit according to medical condition not due to malignant disease.

[c]CT doublet, SOX (S-1 plus oxaliplatin) is an alternative to FOLFOX (infusional 5-fluorouracil, leucovorin and oxaliplatin) or, CAPOX, (capecitabine plus oxaliplatin), and S-1 plus irinotecan is an alternative to FOLFIRI (infusional 5-fluorouracil, leucovorin and irinotecan).

[d]Cetuximab and panitumumab EGFR-targeting monoclonal antibody therapies. Panitumumab is approved first line in combination with FOLFOX and second line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

[e]In patients in need of a rapid reduction of tumour burden because of impending clinical threat, impending organ dysfunction and severe disease-related symptoms a similar strategy can be proposed, although the consensus on the preferred treatment of choice was less strong. For those patients who have *RAS* wt disease, a cytotoxic doublet plus an EGFR antibody is a preferred option. A cytotoxic triplet plus or minus bevacizumab may be an alternative for selected, very fit and motivated patients.

[f]In patients where a bevacizumab-containing regimen was started. In patients where a cetuximab-containing combination was started: pause or less intensive regimen.

[g]If not yet pretreated with EGFR antibody.

BSC, best supportive care; CT, chemotherapy; EGFR, epidermal growth factor receptor; FP, fluoropyrimidine; FOLFOXIRI, infusional 5-fluorouracil, leucovorin, irinotecan and oxaliplatin; mt, mutant; FTD/TPI, trifluridine/tipiracil; wt, wild-type.

Table 3. Summary of recommended regimens

Regimen	Doses and schedules	Trial	Setting	Comparator	ESMO MCBS v1.1	Reference
FOFLOX + bevacizumab	**FOLFOX4** **Oxaliplatin:** 85 mg/m^2 i.v. day 1 **Leucovorin**: 400 mg/m^{2a} i.v. day 1 **5-FU:** 400 mg/m^2 i.v. bolus, then 600 mg/m^2 over 24 h i.v. continuous infusion on day 1 and 2 **Repeated every 2 weeks** **mFOLFOX6** **Oxaliplatin**: 85 mg/m^2 i.v. day 1 **Leucovorin:** 400 mg/m^2 i.v. day 1 **5-FU**: 400 mg/m^2 i.v. bolus on day 1 then 2, 400 mg/m^2 over 46–48 h i.v. continuous infusion **Repeated every 2 weeks** **Bevacizumab:** 5 mg/kg i.v. day 1 **Repeated every 2 weeks**	NO16966 E3200	1st line 2nd line	FOLFOX FOLFOX	1 2	[182] [183]
XELOX ± bevacizumab	**Capecitabine:** 1000 mg/m^2 twice daily PO for 14 days **Oxaliplatin:** 130 mg/m^2 i.v. day1 **Bevacizumab**: 7.5 mg/kg i.v. day 1 **Repeated every 3 weeks**	NO16966	1st line	FOLFOX ± bevacizumab	3 (non-inferiority)	[184]
FOLFIRI + bevacizumab	**FOLFIRI** **Irinotecan:** 150–180 mg/m^2 i.v. over 30–90 min, day 1 **Leucovorin:** 400 mg/m^2 i.v. day 1 **5-FU:** 400 mg/m^2 i.v. bolus on day 1, then 2, 400 mg/m^2 over 46–48 h i.v. continuous infusion **Bevacizumab:** 5 mg/kg i.v. day 1 **Repeated every 2 weeks**	WJOG4407G	1st line	mFOLFOX6 + bevacizumab	3 (non-inferiority)	[185]
FOLFIRI + cetuximab[b]	**FOLFIRI:** **Irinotecan:** 150–180 mg/m^2 i.v. over 30–90 min, day 1 **Leucovorin:** 400 mg/m^2 i.v. day 1 **5-FU:** 400 mg/m^2 i.v. bolus on day 1, then 2, 400 mg/m^2 over 46–48 h i.v. continuous infusion, **Repeated every 2 weeks** **Cetuximab:** 400 mg/m^2 i.v. over 2 h first infusion, then 250 mg/m^2 i.v. over 60 min **weekly**	CRYSTAL FIRE-3	1st line 1st line	FOLFIRI FOLFIRI + bevacizumab	4 3	[37] [142]
FOLFOX + cetuximab[b]	**FOLFOX4** **Oxaliplatin**: 85 mg/m^2 i.v. over 120 min on day 1 **Leucovorin:** 200 mg/m^2 i.v. over 120 min on day 1 **5-FU:** 400 mg/m^2 i.v. bolus, then 600 mg/m^2 over 24 h i.v. continuous infusion on day 1 and 2 **Repeated every 2 weeks** **Cetuximab:** 400 mg/m^2 i.v. over 2 h first infusion, then 250 mg/m^2 i.v. over 60 min **weekly**	TAILOR	1st line	FOLFOX4	4	[181]
FOLFOX + panitumumab	**FOLFOX4** **Oxaliplatin:** 85 mg/m^2 i.v. day 1 **Leucovorin**: 400 mg/m^2 i.v. day 1 **5-FU:** 400 mg/m^2 i.v. bolus, then 600 mg/m^2 over 24 h i.v. continuous infusion on day 1 and 2 **Repeated every 2 weeks**	PRIME	1st line	FOLFOX4	4	[35]
	mFOLFOX6 **Oxaliplatin**: 85 mg/m^2 i.v. day 1 **Leucovorin:** 400 mg/m^2 i.v. day 1 **5-FU**: 400 mg/m^2 i.v. bolus on day 1 then 2, 400 mg/m^2 over 46–48 h i.v. continuous infusion **Repeated every 2 weeks** **Panitumumab:** 6 mg/kg i.v. over 60 min, day 1 **Repeated every 2 weeks**	PEAK	1st line	mFOLFOX6 + bevacizumab	4	[186]

Continued

Table 3. *Continued*

Regimen	Doses and schedules	Trial	Setting	Comparator	ESMO MCBS v1.1	Reference
S-1 + irinotecan + bevacizumab	**SIRB** **S-1:** 40–60 mg/m^2 twice daily PO for 14 days **Irinotecan:** 150 mg/m^2 i.v. day 1 **Bevacizumab:** 7.5 mg/kg i.v. day 1 **Repeated every 3 weeks** **IRIS + bevacizumab** **S-1:** 40–60 mg/m^2 twice daily PO for 14 days **Irinotecan:** 100 mg/m^2 i.v. day 1 and 15 **Bevacizumab:** 5 mg/kg i.v. day 1 and 15 **Repeated every 4 weeks**	TRICOLORE	1st line	FOLFOX/ XELOX + bevacizumab	3 (non-inferiority)	[140, 141]
XELIRI ± bevacizumab	**Capecitabine:** 800 mg/m^2 twice daily PO for 14 days **Irinotecan:** 200 mg/m^2 i.v. day1 **Bevacizumab:** 7.5 mg/kg i.v. day1 **Repeated every 3 weeks**	AXEPT	2nd line	FOLFIRI ± bevacizumab	3 (non-inferiority)	[187]
SOX + bevacizumab	**S-1:** 40 mg/m^2 twice daily PO for 14 days **Oxaliplatin:** 130 mg/m^2 i.v. day1 **Bevacizumab:** 7.5 mg/kg i.v. day1 **Repeated every 3 weeks**	SOFT	1st line	FOLFOX + bevacizumab	3 (non-inferiority)	[188]
FOLFIRI + panitumumab	**FOLFIRI** **Irinotecan:** 150–180 mg/m^2 i.v. over 30–90 min, day 1 **Leucovorin:** 400 mg/m^2 i.v. day 1 **5-FU:** 400 mg/m^2 i.v. bolus on day 1, then 2, 400 mg/m^2 over 46–48 h i.v. continuous infusion **Panitumumab:** 6 mg/kg i.v. over 60 min, day 1 **Repeated every 2 weeks**	2005181	2nd line	FOLFIRI	3	[33]
FOLFIRI + aflibercept	**FOLFIRI** **Irinotecan:** 150–180 mg/m^2 i.v. over 30–90 min, day 1 **Leucovorin:** 400 mg/m^2 i.v. day 1 **5-FU:** 400 mg/m^2 i.v. bolus on day 1, then 2, 400 mg/m^2 over 46–48 h i.v. continuous infusion **ziv-aflibercept:** 4 mg/kg i.v. over 60 min, day 1 **Repeated every 2 weeks**	VELOUR	2nd line	FOLFIRI + placebo	1	[164]
FOLFOXIRI + bevacizumab	**FOLFOXIRI** **Irinotecan:** 165 mg/m^2 i.v. day 1 **Oxaliplatin:** 85 mg/m^2 i.v. day 1 **Leucovorin:** 400 mg/m^2 i.v. day 1 **5-FU:** 3, 200 mg/m^2 over 46–48 h i.v. continuous infusion starting on day 1 **Bevacizumab:** 5 mg/kg i.v. day 1 **Repeated every 2 weeks**	TRIBE	1st line	FOLFIRI + bevacizumab	3	[52]
FOLFIRI + ramucirumab	**FOLFIRI** **Irinotecan:** 150–180 mg/m^2 i.v. over 30–90 min, day 1 **Leucovorin:** 400 mg/m^2 i.v. day 1 **5-FU:** 400 mg/m^2 i.v. bolus on day 1, then 2, 400 mg/m^2 over 46–48 h i.v. continuous infusion **Ramucirumab:** 8 mg/kg i.v. over 60 min, day 1 **Repeated every 2 weeks**	RAISE	2nd line	FOLFIRI + placebo	1	[160]

Continued

Table 3. *Continued*

Regimen	Doses and schedules	Trial	Setting	Comparator	ESMO MCBS v1.1	Reference
Cetuximab[b]	**Cetuximab:** 400 mg/m^2 i.v. over 2 h first infusion, then 250 mg/m^2 i.v. over 60 min **weekly** plus BSC	CO.17	3rd line	BSC	4	[189, 190]
Panitumumab	**Panitumumab:** 6 mg/kg i.v. once **every 2 weeks.**	20020408	3rd line	BSC	2	[34, 191, 192]
		20100007	3rd line	BSC	4	
Trifluridine/tipiracil (FTD/TPI)	**FTD/TPI:** 35 mg/m^2 up to a maximum dose of 80 mg per dose PO twice daily days 1–5 and 8–12, repeated **every 28 days**	RECOURSE	Late line	Placebo	2	[174, 193]
		TERRA	Late line	Placebo	1	[175]
Regorafenib	**Regorafenib:** 160 mg PO daily days 1–21, repeated **every 28 days**	CORRECT	Late line	Placebo	1	[168, 169]
		CONCUR	Late line	Placebo	3	[171]

[a]Two hundred milligrams per metre square for L-form.

[b]Different dose and schedule for cetuximab (500 mg/m^2 i.v. over 2 h, day 1, every 2 weeks) can be applicable [194].

BSC, best supportive care; FOLFIRI, infusional 5-fluorouracil, leucovorin and irinotecan; FOLFOX, infusional 5-fluorouracil, leucovorin and oxaliplatin; FOLFOXIRI, infusional 5-fluorouracil, leucovorin, irinotecan and oxaliplatin; IRIS, S-1 plus irinotecan; i.v., intravenous; MCBS, magnitude of clinical benefit score; PO, by mouth (orally); SOX, S-1 plus oxaliplatin; FTD/TPI, trifluridine/tipiracil; XELIRI, capecitabine plus irinotecan (CAPIRI); XELOX, capecitabine plus oxaliplatin (CAPOX).

except in the CRYSTAL trial where a benefit in ORR was observed, but not in PFS or overall survival. There was a similar trend in the second-line 20 050 181 trial for ORR. Furthermore, individual patient data for patients with right-sided tumours from the FIRE-3 trial suggested that patients with right-sided *RAS* wt tumours might benefit from chemotherapy plus bevacizumab compared with cetuximab in terms of overall survival but not ORR. This suggests that there may be a subset of patients with right-sided *RAS* wt tumours that might benefit from treatment with chemotherapy plus bevacizumab in terms of PFS and overall survival. Thus, the individual trial findings and the pooled analysis data provided the foundation for a proposal that a distinction needed to be made between the systemic therapy approaches used for the treatment of mCRC patients who present with right- versus left-sided primary tumours.

The Asian experts were asked to provide responses to the following four recommendation statements from the pooled analysis manuscript [11] as part of the second pre-meeting survey (May 2017) with the following levels of agreement:

a. Reinforce the use of EGFR antibody therapy in patients with mCRC and left-sided *RAS* wt tumours [A=100%].
b. Promote the idea that patients with right-sided *RAS* wt tumours might be better treated with chemotherapy alone or chemotherapy plus bevacizumab —except maybe if the goal is tumour size reduction as the ORRs were higher (but not PFS and overall survival) [A=100%].
c. Emphasise that in the absence of data on specific treatment sequences, there is no reason that EGFR-antibody therapy should be avoided in cases of disease progression or treatment intolerance independent of primary tumour location [A=100%].
d. Promote the concept of a 'continuum of care' and the sequential use of all therapies, including bevacizumab where appropriate, in the treatment of patients with mCRC [A=100%].

The recommendations from the meeting provided by the four ESMO experts (AC, FC, JYD and JT) for the treatment of patients with left- versus right-sided primary colorectal tumours are presented in Figure 2A and B, together with the levels of agreement provided by experts from each of the six Asian countries for each of the ESMO expert treatment recommendations. The precise voting of the Asian experts can be seen in supplemen-tary Figure S1A and B, available at *Annals of Oncology* online.

Thus, the agreed systemic therapy choices according to the treatment algorithm for Asian patients with unresectable metastatic disease are presented in Figure 1 and Table 2, with consideration of the impact of left- versus right-sided primary tumour location included. The specific regimen choices for Asian patients supported by the appropriate trial references and ESMO magnitude of clinical benefit score are summarised in Table 3. The summary of the final Asian guideline recommendations (Table 1) includes retrospective amendments to **recommendations 13 and 18, and consensus statements A1a, A2a and B1a** to include consideration of primary tumour location, that were approved by all the Asian experts with the same levels of agreement as they assigned to the original three recommendations (see above and supplementary Table S5, available at *Annals of Oncology* online). These represent the final voting recommendations of the Asian experts.

Discussion

Conclusions

The results of the voting by the Asian experts showed high concordance (supplementary Tables S2–S5, available at *Annals of Oncology* online) with the ESMO consensus recommendations published in 2016 [9]. In terms of level of agreement, there were no votes of less than a B (accept with some reservation)

(supplementary Tables S2–S5, available at *Annals of Oncology* online). Level B agreement was assigned to 'recommendation 5' by one country (supplementary Table S1, available at *Annals of Oncology* online), to 'recommendation 12c' by two countries, to 'recommendation 12f' by two countries, to 'recommendation 15a, b, c and d' by one country (supplementary Table S3, available at *Annals of Oncology* online) and to 'recommendations 19a and c' by one country (supplementary Table S4, available at *Annals of Oncology* online). All the other votes were for level A agreement (accept completely), across all the other recommendations. In terms of the 17 'consensus recommendations' there was at least one country that assigned a level B agreement and this was to 'consensus recommendations A1a, A1b, A1c, A1d and A1e'. Two other countries also assigned level B agreement to 'consensus recommendation A1e' (supplementary Table S5, available at *Annals of Oncology* online). All the other votes across all of the remaining 11 consensus recommendations were for level A agreement (supplementary Table S5, available at *Annals of Oncology* online). Thus, an overall consensus was reached. A 100% of the Asian experts agreed (accepted) either completely or with some reservation the ESMO recommendations, with some slight revision of the text and the deletion of the original ESMO 'recommendation 12g'. The recommendations were modified retrospectively Tables 1 and 2 and Figure 1 to include consideration of primary tumour location (left- versus right-side) in the strategic treatment of Asian patients with mCRC. As mentioned previously the levels of agreement provided by each of the Asian experts were based on the available 'scientific' evidence, and were independent of the approval and reimbursement status of certain drugs (including biologics) in their individual countries. A summary of the approval and reimbursement status of the recommended drugs, as of July 2017, is presented for each participating country in supplementary Figure S2A–D, available at *Annals of Oncology* online, and will obviously impact on some of the treatment strategies that can be adopted by certain countries.

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