ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 19–33, 2019
doi:10.1093/annonc/mdy502
Published online 22 November 2018

SPECIAL ARTICLE

Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic gastric cancer: a JSMO–ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS

K. Muro[1*], E. Van Cutsem[2], Y. Narita[1], G. Pentheroudakis[3], E. Baba[4], J. Li[5], M.-H. Ryu[6], W. I. Wan Zamaniah[7], W.-P. Yong[8], K.-H. Yeh[9,10], K. Kato[11], Z. Lu[12], B. C. Cho[13], I. M. Nor[14], M. Ng[15] L.-T. Chen[16], T. E. Nakajima[17], K. Shitara[18], H. Kawakami[19], T. Tsushima[20], T. Yoshino[18], F. Lordick[21,22], E. Martinelli[23], E. C. Smyth[24], D. Arnold[25], H. Minami[26], J. Tabernero[27] & J.-Y. Douillard[28]

[1]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [2]Digestive Oncology, University Hospitals Leuven, Leuven, Belgium; [3]Department of Medical Oncology, University of Ioannina, Ioannina, Greece; [4]Department of Comprehensive Clinical Oncology, Kyushu University, Fukuoka, Japan; [5]Department of Oncology, Tongji University affiliated East Hospital, Shanghai, China; [6]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [7]Department of Clinical Oncology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [8]Department of Haematology-Oncology, National University Cancer Institute, Singapore, Singapore; [9]Department of Oncology, National Taiwan University Hospital, Taipei; [10]National Taiwan University Cancer Center, National Taiwan University College of Medicine, Taipei, Taiwan; [11]Division of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [12]Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing, China; [13]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; [14]Department of Radiotherapy & Oncology, General Hospital, Kuala Lumpur, Malaysia; [15]Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore; [16]National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan; [17]Department of Clinical Oncology, School of Medicine, St. Marianna University, Kawasaki; [18]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa; [19]Department of Medical Oncology, Faculty of Medicine, Kindai University, Osaka; [20]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan; [21]University Cancer Centre Leipzig, Leipzig; [22]1st Department of Medicine (Hematology and Medical Oncology), University Hospital Leipzig, Leipzig, Germany; [23]Department of Precision Medicine – Medical Oncology, Università degli Studi della Campania L Vanvitelli, Napoli, Italy; [24]Department of Oncology, Cambridge University Hospital NHS Foundation Trust, Cambridge, UK; [25]Asklepios Tumorzentrum Hamburg, Asklepios Klinik Altona, Hamburg, Germany; [26]Department of Medical Oncology and Hematology, Kobe University Hospital, Kobe, Japan; [27]Medical Oncology Department, Vall d' Hebron University Hospital, Vall d'Hebron Institute of Oncology (V.H.I.O.), Barcelona, Spain; [28]ESMO, Lugano, Switzerland

Correspondence to: Prof. Kei Muro, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan. Tel: +81-52-762-6111 (ext. 3777); Fax: +81-52-764-9855; E-mail: kmuro@aichi-cc.jp

The most recent version of the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of gastric cancer (GC) was published in 2016, and covered the management and treatment of local, locoregional, locally advanced and metastatic disease. At the ESMO Asia Meeting in November 2017 it was decided by both ESMO and The Japanese Society of Medical Oncology (JSMO) to convene a special guidelines meeting immediately after the JSMO Annual Meeting in 2018. The aim was to adapt the ESMO 2016 guidelines to take into account the ethnic differences associated with the treatment of metastatic GC in Asian patients. These guidelines represent the consensus opinions reached by experts in the treatment of patients with metastatic GC representing the oncological societies of Japan (JSMO), China (CSCO), Korea (KSMO), Malaysia (MOS), Singapore (SSO) and Taiwan (TOS). 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: metastatic gastric cancer, Pan-Asian, consensus, ESMO guidelines

Introduction

Gastric cancer (GC) was the third leading cause of cancer death in 2012 for both men and women, with 723 000 recorded deaths accounting for 8.8% of cancer deaths worldwide [1]. The highest incidence and mortality rates for both men and women were reported for Eastern and Western Asia, Latin America and some Eastern European countries [2]. The incidence rates (cases/100 000 people) for men in Japan's Miyagi Prefecture and Korea of 66.7 and 64.6, respectively, were both more than twice those of the next highest incidence rate of 30.4 that was reported for the Golestan province of Iran. For women, the incidence rates in Japan of 22.8 and Korea of 25.4 were 60% higher than the next highest rates, which were in Ecuador and Costa Rica and were 15.0 for each country [2]. Thus, GC is a major healthcare challenge across Asia and particularly Eastern Asia.

GC is classified as either cardia GC (CGC) or non-cardia GC (NCGC) depending on the site/location within the stomach (proximal or distal), and the incidence of each subtype is influenced by regional variations in the risk factors for each. The highest regional rates for both CGC and NCGC are in Eastern and Southeastern Asia [3]. Chronic infection with *Helicobacter pylori* (*H. pylori*) accounts for ∼90% of the cases of distal NCGC worldwide [4]. Other influences are thought to include availability of fresh fruits and vegetables, dietary patterns and methods of food preservation [4].

However, since the middle of the 20th century, both the incidence and mortality rates for GC have been declining in North America, high-income countries in Europe and more recently in many other countries, including those in Asia. These trends have been dominated by a decline in the occurrence of NCGC and are thought to be attributable to the decline in *H. pylori* infections [5] due to improved sanitation and the availability of antibiotics. In addition, the availability of fresh produce, less reliance on salt-preserved foods [6], and a reduction in smoking may also have contributed to the declines [7]. Conversely, the rates of CGC and cancers of the gastro-oesophageal junction (GEJ) are increasing in the United States, and many European countries [8–10], which possibly reflects the increase in visceral obesity and gastro-oesophageal reflux in the populations of these countries. Although the clinical behaviour of GC is distinct in each country as stated above, establishing an integrated consensus for the treatment and management of patients with GC across continents is thought to be valuable.

Guidelines for the prevention, screening, treatment and management of patients with GC in Asia have been published previously [11–17]. The ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with GC have also recently been published [18], and a decision was taken by the ESMO and JSMO to use these latest ESMO guidelines to develop guidelines for the treatment and management of metastatic GC (mGC) in patients of Asian ethnicity. As a result, a 1-day, face-to-face, working meeting was convened on the 22 July 2018 in Kobe Japan immediately after the 16th Annual Meeting of the JSMO, to finalise this process. Finalisation of the Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic oesophageal cancer took place at the same meeting and will be published separately [19].

Methodology

This Pan-Asian adaptation of the ESMO guidelines was prepared in accordance with the processes and format developed for the preparation of the first Pan-Asian adapted ESMO guidelines for the management of patients with metastatic colorectal cancer [20].

Composition of expert panel

The international panel of experts was selected according to their demonstrable knowledge of the field of gastric and oesophageal cancer patient treatment and management in terms of publications and/or their participation in the development of national or international treatment guidelines. More specifically this included 10 expert members of the JSMO, 8 expert members from the ESMO and 2 experts each from the oncological societies of China (CSCO), Korea, (KMSO), Malaysia (MOS), Singapore (SSO) and Taiwan (TOS). Only 2 of the 10 expert members from the JSMO (EB and KK) were allowed to vote on the recommendations together with the 2 experts from each of the 5 other Asian oncological societies.

Provisional statements

A set of preformulated topics and eight recommendations for the treatment of mGC, based on those in the latest ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of GC [18], were circulated, before the meeting, to each of the 12 Asian experts representing the 6 Asian oncological societies to gather their comments and input on each of the recommendations. Specific emphasis was placed on current agreement with the published data used for the recommendations in their countries, including the data generated from studies in Asian patients, together with the applicability of novel clinical study data to current practice in their countries. Consideration was to be made independently of the actual access to, and availability of, the respective diagnostic tools and treatments in their respective countries. The Asian experts were specifically asked 'Is this recommendation adaptable for use in your country?'. The 12 experts were also asked to provide details of the reasoning behind their responses and the relevant references to support their decisions.

Voting process

A modified Delphi process was used to develop each individual statement before the final discussion and final voting process at the face-to-face working meeting in Kobe. The 12 Asian experts 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 reservation; D = reject with some reservation and E =reject completely (Table 1). An adapted version of the 'Infectious Diseases Society of America-United States Public Health Service Grading System' [21] was used to define the level of evidence and strength (grade) of each recommendation proposed by the group, as for all of the ESMO Consensus and ESMO Clinical Practice Guidelines (Table 1), and are given in the text in square brackets after each recommendation together with details of the levels of agreement. Most statements on the

Table 1. Voting on levels of agreement and definition of levels of evidence and grades of recommendation used by the panel of Asian experts in evaluating the ESMO consensus guidelines for the management of patients with metastatic gastric cancer of Asian ethnicity

Voting on level of agreement	
A	Accept completely
B	Accept with some reservation
C	Accept with major reservation
D	Reject with some reservation
E	Reject completely
Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (low methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies of case-control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk of the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

level of agreement were based on peer-reviewed manuscript data or peer-reviewed abstract data, 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 remaining 16 experts, 8 from the JSMO and 8 from the ESMO were there to offer expert opinion at the face-to-face meeting, with 1 non-voting member of the JSMO (KM) and 1 non-voting member of the ESMO (EVC) co-chairing the meeting.

Final consensus statements

A consensus was considered to have been achieved when $\geq$80% of experts voted to accept completely or accept with reservation a specific recommendation. A recommendation was considered to have been rejected when >80% of the voting members indicated 'reject completely' or 'reject with reservation'. For recommendations where a consensus was not reached initially the entire panel of 12 Asian experts was invited to discuss and modify the recommendation(s) at the face-to-face meeting, and a second round of voting was conducted. If still no consensus could be reached, the recommendation could be modified one more time, and a third and last vote was conducted to determine the definitive acceptance or rejection of a recommendation.

Results

In the initial pre-meeting survey, the 12 experts representing the oncological societies of the 6 Asian countries (Japan, China, Korea, Malaysia, Singapore and Taiwan) reported on the applicability of the eight recommendations for the management and treatment of mGC from the 2016 ESMO Clinical Practice Guidelines [18]. These recommendations were made in the categories:

1. Biomarkers
2. Hereditary cancer
3. Diagnosis and pathology
4. First-line treatment (4a, b, c and d)
5. Treatment of elderly patients (5a and b)
6. Second- and further-line treatment (6a, b and c)
7. Personalised medicine
8. Specific situations (8a and b)

and for the purposes of the evaluation and voting process were numbered 1–8 with the subcategories assigned a letter code (a, b, c, etc.). An unqualified response of YES in the pre-meeting survey equated with 'accept completely' in the final voting, i.e. A = 100%. Following the initial survey, agreement was not reached between the 6 Asian countries on recommendations 2, 4a, c and d, 5a and b, 6c and 8a (supplementary Table S1, available at *Annals of Oncology* online). At the face-to-face meeting in Kobe, the 12 Asian experts in the treatment of GC were asked to discuss and to vote again on these recommendations. Voting on recommendations 1a, 3, 4 b, 6a and e (the original 'recommendation 6d'), 7 and 8b was not necessary, although additional recommendations concerning biomarkers were made. 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, beside each of the eight recommendations. Where changes to the original text have been made, including the addition of new subcategories and in some cases the complete revision of an existing recommendation, these are emphasised in bold both in the main text of the article and Table 2, and reference made to the change in the text as

Table 2. Summary of Asian recommendations

Recommendation 1: biomarkers

1a. Immunohistochemistry and (fluorescence) *in situ* hybridisation should be conducted to assess HER2 protein expression and *HER2* gene amplification, respectively, with the aim of selecting patients with metastatic disease for treatment with a trastuzumab-containing regimen [A = 100% and I, A].

1b. *UDP glucuronosyltransferase 1 family polypeptide A1* (*UGT1A1*) genotyping remains an option and is recommended to be carried out in patients with a suspicion of UGT1A1 deficiency or in patients where an irinotecan dose of >180 mg/m^2 per administration is planned* [A = **100**% **and III, C]**

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

Recommendation 2: hereditary cancer

2. If a familial cancer syndrome such as HDGC is suspected, **ideally**, referral to a geneticist for assessment is recommended based on international clinical guidelines [A = 100% and V, B].

Recommendation 3: diagnosis and pathology

3. Diagnosis should be made from a gastroscopic or surgical biopsy reviewed by an experienced pathologist, and histology should be reported according to the WHO criteria [A = 100% and IV, C].

Recommendation 4: first-line treatment

4a-1. Doublet platinum/fluoropyrimidine combinations are recommended for fit patients with advanced gastric cancer [A = 100% and I, A].

4a-2. A triplet regimen comprising platinum/fluoropyrimidine/taxane is an option for fit patients with advanced gastric cancer [A = 83%, B = 17% and I, A].

4b. Patients with inoperable locally advanced and/or metastatic (stage IV) disease should be considered for systemic treatment (chemotherapy), which has shown improved survival and quality of life compared with best supportive care alone [A = 100% and I, A]. However, comorbidities, organ function and PS must always be taken into consideration [II, B].

4c. Capecitabine or S-1 can be used as an alternative to infusional 5-FU in doublet regimens [A = 100% and I, A].

Recommendation 5: treatment of elderly patients

5. Single-agent fluoropyrimidine treatment can be recommended for frail elderly patients [A = 100% and III, B]. A doublet fluoropyrimidine and platinum regimen is recommended for fit elderly patients [A = 100% and III, B].

Recommendation 6: second- and further-line treatment

6a. Second-line chemotherapy with a taxane (docetaxel, paclitaxel), or irinotecan, or ramucirumab as a single agent or in combination with paclitaxel is recommended for patients who are of PS 0–1 [A = 100% and I, A].

6b. In patients **treated with chemotherapy which stopped before progression and who have not progressed within** 3 months it may be appropriate to consider **the reintroduction o**f the same drug combination **as long as any toxicity issues have been resolved** [A = 100% and IV, C].

6c. Nivolumab, pembrolizumab or **trifluridine/tipiracil (TAS-102) should be considered as third- or further-line treatment, if approved. Irinotecan or a taxane (if not used in the earlier lines) are also options for third- or further-line treatment [A = 100% and V, C]. Apatinib may also be considered but only in China [A = 100% and I, A].**

6d. In patients with symptomatic locally advanced or recurrent disease, hypofractionated radiotherapy is an effective and well-tolerated treatment modality that may palliate bleeding, obstructive symptoms or pain [A = 100% and III, B].

Recommendation 7: personalised medicine and targeted therapy

7a. Trastuzumab is recommended in conjunction with platinum- and fluoropyrimidine-based chemotherapy for patients with HER2-positive advanced gastric cancer [A = 100% and I, A].

Recommendation 8: specific situations

8a. Metastasectomy: **gastrectomy in patients with stage IV disease or metastasectomy are not routinely recommended** [A = 100% and I, A].

8b. Peritoneal metastases: In patients with peritoneal metastases, the use of cytoreductive surgery plus HIPEC has been studied, but this approach cannot yet be recommended outside the context of clinical research [A = 100% and IV, C].

5-FU, 5-fluorouracil; HER2, human epidermal growth factor receptor-2; HDGC, hereditary diffuse gastric cancer; HIPEC, hyperthermic intraperitoneal chemotherapy; PS, performance status; S-1, tegafur/gimeracil/oteracil; TAS-102, trifluridine/tipiracil; UGT1A1, UDP glucuronosyltransferase 1 family polypeptide A1; WHO, World Health Organization.

appropriate. In parallel, the final voting patterns of the representatives of each of the participating regions for the ESMO recommendations at the face-to-face meeting in Kobe are presented in supplementary Table S2, available at *Annals of Oncology* online.

Recommendation 1: biomarkers

1a. Immunohistochemistry and/or (fluorescence) in situ hybridisation should be conducted to assess HER2 protein expression and HER2 gene amplification, respectively, with the aim of selecting patients with metastatic disease for treatment with a trastuzumab-containing regimen [A = 100% and I, A].

1b. UDP glucuronosyltransferase 1 family polypeptide A1 (UGT1A1) genotyping remains an option and is recommended to be carried out in patients with a suspicion of UGT1A1 deficiency or in patients where an irinotecan dose of >180 mg/m^2 per administration is planned* **[A = 100% and III, C]**

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

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendation 1a' above that the human epidermal growth factor receptor-2 (HER2) status (HER2 positivity) of the tumours of all patients with mGC should be established at the time of diagnosis. This opinion was based on data from the randomised, phase III ToGA trial [22] in which HER2 positivity (increased HER2 expression or *HER2* gene amplification) was observed in 22.1% of the tumour samples analysed from patients with advanced GC or advanced cancer of the GEJ [23]. The rates of HER2 positivity were similar for European and Asian patients at 23.6% and 23.9%, respectively [23]. Trastuzumab plus chemotherapy was shown to significantly improve overall survival (OS) in patients with HER2-positive tumours compared with those who received chemotherapy alone (OS 16.0 versus 11.8 months, hazard ratio 0.65, 95% confidence interval 0.51–0.80) and is recommended in combination with chemotherapy for the treatment of patients with HER2 immunohistochemistry (IHC) 2+ with fluorescence *in situ* hybridisation-positive or IHC 3+ disease [Magnitude of Clinical Benefit Scale (MCBS) 5] [22]. This benefit of trastuzumab in HER2-positive patients was confirmed for Asian patients in a subgroup analysis of 101 HER2-positive Japanese patients included in the ToGA trial [24], and in a randomised, controlled trial of 85 Chinese patients [25]. Comparable antitumour activity was also seen in the non-randomised phase II Japanese HERBIS-1 study in which patients with HER2-positive tumours were treated with trastuzumab tri-weekly in combination with tegafur/gimeracil/oteracil (S-1) and cisplatin [26]. Assessment of HER2 positivity with a view to selecting patients for treatment with a trastuzumab-containing regimen is used routinely in Japan, China, Korea Taiwan and Singapore for patients with inoperable mGC, and is recommended by the Japanese gastric treatment guidelines [12], CSCO, the Chinese Anticancer Society, the Korean Clinical Practice Guidelines [14, 15] and the Taiwan Cooperative Oncology Group (TCOG) Clinical Practice Guidelines for GC. For details of further trials, see 'recommendation 7'.

The experts also agreed completely [A = 100%] with the addition of 'recommendation 1b' above, most of the wording for which was taken from the Pan-Asian adapted ESMO guidelines for the management of patients with metastatic colorectal cancer [20]. The enzyme activity of UGT1A1 is known to be closely associated with genetic polymorphisms of *UGT1A1*. In Asian patients, the frequency of the *UGT1A1* *28 variant is much lower than that in Caucasian patients, whilst the converse is true for the *UGT1A1* *6 variant [27]. Some Japanese studies [28, 29] have reported that *UGT1A1* *6 or *28 homozygous genotypes increase the incidence of severe neutropenia but not diarrhoea, and Cheng et al. have verified the association between *UGT1A1* *6/*6 alleles and severe neutropenia among Asian populations in a meta-analysis [30]. It is estimated that ~10% of Japanese patients are either homozygous or simultaneously heterozygous for the *UGT1A1* *6 or *28 alleles associated with irinotecan-induced toxicities [31, 32]. Thus, for patients known to have such a genetic background, irinotecan dose reduction is strongly recommended, and for patients with homozygous genotypes, the maximum tolerated dose is considered to be 150 mg/m^2 [29, 30].

In addition, the Pan-Asian experts proposed that gastric tumours may be optionally tested for microsatellite instability (MSI) and mismatch repair deficiency (dMMR) with a view to predicting the clinical benefit of immune check-point inhibitors (ICIs), once they become available to patients [33]. At the present time, the opinion is that the tumours of patients with mGC do not need to be routinely tested for programmed death-ligand 1 (PD-L1), tumour mutation burden (TMB) and Epstein Barr virus (EBV). However, PD-L1, TMB and EBV may be considered as potential biomarkers for the use of ICIs in the future [34–37].

Recommendation 2: hereditary cancer

2. If a familial cancer syndrome such as hereditary diffuse GC (HDGC) is suspected, ***ideally,*** *referral to a geneticist for assessment is recommended based on international clinical guidelines [A = 100% and V, B].*

The Asian experts accepted completely [A = 100%] the statement in 'recommendation 2' following considerable discussion (see initial voting in supplementary Table S1, available at *Annals of Oncology* online) and a modification to the text to include the word ideally (see bold text above). HDGC accounts for 1%–3% of the total GC incidence worldwide [38]. However, such incidence data are not available for Asia. In Japan, HDGC families with a *CDH1* germline mutation or a large deletion in the *CDH1* gene have been reported [39–41]. However, overall in the case of the 6 Asian countries represented by the experts, HDGC is considered to be very rare and access to a geneticist who specialises in GC is difficult in most of the six countries.

Recommendation 3: diagnosis and pathology

3. Diagnosis should be made from a gastroscopic or surgical biopsy reviewed by an experienced pathologist, and histology should be reported according to the World Health Organization (WHO) criteria [A = 100% and IV, C].

The Asian experts accepted completely [A = 100%] the ESMO recommendation on 'diagnosis and pathology' taken from the ESMO 2016 guidelines [18]. Patients in Asian countries are frequently diagnosed with earlier stage disease than patients in non-Asian countries. In Japan and Korea where the incidences of GC are the highest in the world, national screening programmes for routine GC screening are available [2]. Ninety percent of GCs are adenocarcinomas which are subdivided according to histological appearance into diffuse (undifferentiated) and intestinal (well-differentiated) carcinomas according to the Lauren classification [42]. The Japanese Classification of Gastric Carcinoma (JCGC) (15th edition or 3rd edition in English [43]) is also widely used in Japan in terms of histological diagnosis and differs in some respects from the WHO and Lauren classifications, e.g. poorly cohesive carcinoma in the WHO classification, includes non-solid type poorly differentiated adenocarcinoma and signet-ring cell carcinoma in JCGC criteria. The Cancer Genome Atlas (TCGA) molecular subtyping project has identified four principal GC

subtypes [44, 45]. Comprehensive profiling of GCs from 207 Japanese patients with a 435-gene panel showed Japanese patients to be consistent with these four molecular subtypes but to have significantly fewer tumours with MSI (8% versus 21%) and more genome stable tumours (30% versus 20%) than the TCGA GC classification. In addition, actionable genetic alterations were not specific and were widely observed throughout the four TCGA subtypes [46]. The Asian Cancer Research Group (ACRG) has also classified patients with GC into four subtypes according to molecular profiling [47]. Both the TCGA and ACRG classifications have identified a group of MSI-high tumours, but differ in the other subtypes. The MSI-high and EBV-positive GC subtypes has been shown to be highly sensitive to immunotherapy, whilst patients with the ACRG epithelial-to-mesenchymal transition GC subtype may not respond to single-agent antiprogrammed death-1 (PD-1) receptor therapy [36]. In addition, the ACRG subtypes have prognostic value, but the TCGA GC subtypes do not. Three major subtypes of GC have been identified in patients from Singapore and Australia [48]. As for the ESMO 2016 Guidelines [18], the current guidelines document does not consider rarer gastric malignancies, such as gastrointestinal stromal tumours, lymphomas and neuroendocrine tumours.

Recommendation 4: first-line treatment

4a-1. Doublet platinum/fluoropyrimidine combinations are recommended for fit patients with advanced GC [A = 100% and I, A].

4a-2. A triplet regimen comprising platinum/fluoropyrimidine/taxane is an option for fit patients with advanced** GC **[A = 83%, B = 17% and I, A].

4b. Patients with inoperable locally advanced and/or metastatic (stage IV) disease should be considered for systemic treatment (chemotherapy), which has shown improved survival and quality of life compared with best supportive care (BSC) alone [A = 100% and I, A]. However, comorbidities, organ function and performance status (PS) must always be taken into consideration [II, B].

4c. Capecitabine is associated with improved OS compared with infused 5-FU within doublet and triplet regimens [I, A], was revised to read ***Capecitabine or S-1 can be used as an alternative to infusional 5-FU in doublet regimens [A = 100% and I, A].***

4d. DCF in a 3-weekly regimen was associated with improved OS, but also added significant toxic effects including increased rates of febrile neutropenia [I, C]. This recommendation was to be removed.

The Pan-Asian panel of experts agreed with and accepted completely [A = 100%] and accepted completely [A = 83%] or with some reservation [B = 17%] 'recommendation 4a' for the first-line treatment of HER2-negative mGC (stage IV) taken from the ESMO 2016 guidelines [18] once it had been separated into two statements 4a-1 and 4a-2. The words 'or triplet' were removed from the original statement to generate 'recommendation 4a-1' and a new recommendation was inserted concerning the use of triplet chemotherapy combinations 'recommendation 4a-2' (see bold text). The representatives of JSMO could only accept with some reservation [B] the new 'recommendation 4a-2'. 'Recommendation 4b' was accepted completely [A = 100%] and 'recommendation 4c' was accepted completely [A = 100%] once it had been revised as indicated by the bold text above. 'Recommendation 4d' was deleted as it was considered to have been incorporated into 'recommendation 4a-2', and again this revision was accepted completely [A = 100%].

These recommendations and the adaptations to the original ESMO 2016 recommendations were based on the fact that systemic chemotherapy has been shown to improve survival and quality of life compared with BSC alone, in patients with GC [49–51]. Typically in Asia, first-line therapy is a platinum/fluoropyrimidine doublet based on the demonstrated improvement in response and survival compared with fluoropyrimidine alone in Asian patients with GC [52, 53] (Figure 1). Both cisplatin and oxaliplatin have been shown to have similar efficacy as components of doublet and triplet regimens for the treatment of Western and Asian patients with mGC [54–57]. However, oxaliplatin is the preferred choice due to its favourable safety profile and ease of administration. Of the three available fluoropyrimidines, 5-fluorouracil (5-FU), capecitabine and S-1, capecitabine tends to be favoured due to its ease of administration and its demonstrated non-inferiority to infusional 5-FU in triplet and doublet regimens [55, 58, 59]. Although, 5-FU is also routinely used in Asian countries, especially for patients who cannot manage oral intake or have massive ascites. Subset analyses of the data from the AVAGAST and ToGA trials also showed capecitabine plus cisplatin to be well tolerated in Japanese patients [60]. A meta-analysis found no differences in OS or progression-free survival (PFS) for capecitabine-based versus 5-FU-based regimens, S-1-based versus 5-FU-based regimens and S-1-based versus capecitabine-based regimens [61]. Moreover, the effects were similar in Asian and Western patient subgroups [61]. S-1 has similar efficacy to capecitabine both as a single agent [62] and in platinum doublets [61, 63] but with a lower frequency of relevant adverse events.

The triplet regimen of docetaxel, cisplatin, 5-FU (DCF) has been shown to improve OS when compared with the doublet regimen of cisplatin and 5-FU, however, its use is limited due to significant toxicity [64]. A small randomised phase II study of modified DCF (mDCF) compared with DCF [65] demonstrated an improvement in survival for mDCF, but although the toxicity was less, it still remained significant with a 22% hospitalisation rate. However, recent data from the Japanese phase III JCOG1013 trial show the addition of docetaxel to doublet S-1 and cisplatin chemotherapy to fail to improve OS in patients with advanced GC [66]. mDCF therefore may be considered in selected patients, supported by two recent Asian trials [67, 68].

Also, although a meta-analysis has demonstrated a significant benefit from the addition of an anthracycline to a platinum/fluoropyrimidine doublet [59], the addition of anthracyclines to a platinum/fluoropyrimidine doublet did not lead to improved response or survival in Asian patients [69], and is not recommended. Trials of non-platinum containing fluoropyrimidine doublets with docetaxel [70] or paclitaxel [71] conducted in Asian patients or irinotecan in trials conducted in Western patients [72, 73] have also shown similar efficacy to doublet platinum/fluoropyrimidine combinations. However, these doublets

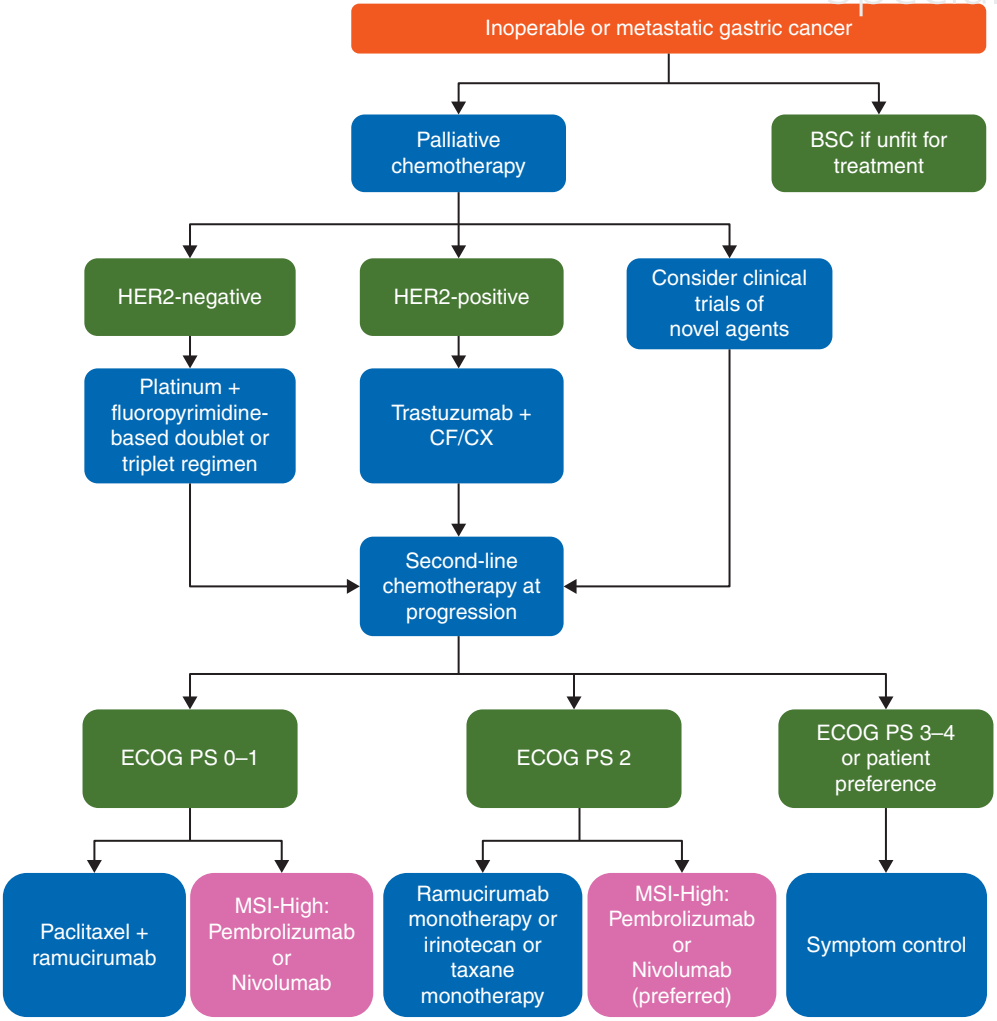


Figure 1. First- and second-line treatment options for patients with metastatic gastric cancer. BSC, best supportive care; CF, cisplatin and 5-fluorouracil; CX, cisplatin and capecitabine; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; MSI, microsatellite instability; PS, performance status.

are not routinely used in Asia, as taxanes and irinotecan are typically reserved for use in the second- and third-line treatment settings.

Recommendation 5: treatment of elderly patients

5-a. Regimens that have been specifically addressed in phase II trials in elderly patients, with comparable survival results, include capecitabine and oxaliplatin, FOLFOX, single-agent capecitabine and S-1 (in Asian patients) [III, B], was revised to read ***Single-agent fluoropyrimidine treatment can be recommended for frail elderly patients [A = 100% and III, B]. A doublet fluoropyrimidine and platinum regimen is recommended for fit elderly patients [A = 100% and III, B].***

5-b. The FLOT regimen is associated with a trend towards improved PFS but also with increased toxicity [II, B]. This recommendation was to be removed.

The Pan-Asian panel of experts agreed with and accepted completely [A = 100%] the reworded version of 'recommendation 5a' above, the original of which was taken from the ESMO 2016 guidelines [18]. The revisions were made to reflect the current situation for the treatment of mGC in Asian patients. It was agreed unanimously that 'recommendation 5b' should be deleted as it was considered to have been incorporated into 'recommendation 4a-2'. In Asia, the regimens for the treatment of elderly patients with mGC have evolved based on the results of phase II trials in elderly patients and subgroup analyses of elderly patients included in phase III trials. A Japanese phase II trial has shown the median PFS and OS for patients with mGC aged >75 years achieved with single-agent S-1 [74] to be comparable with those achieved in the S-1 treatment arm of the phase III SPIRITS trial in patients aged 20-74 years [53]. A subgroup analysis of the Japanese phase III JFMC36-0701 trial showed a similar benefit for patients aged ≥75 and <75 years treated with S-1 [75], whilst a Korean phase II trial in patients aged ≥65 years showed capecitabine and S-1 to be equally effective [62]. In Taiwan, high-dose fluorouracil and leucovorin therapy has been widely used for over 20 years, and is widely used for the treatment of elderly patients [17, 76, 77] and is listed in the TCOG GC Guidelines for Taiwan [78] (also cited in reference [17]), and in the National Taiwan University Hospital GC guidelines. Dose attenuated

capecitabine oxaliplatin (CAPOX) [79] and 5-FU, leucovorin and oxaliplatin (FOLFOX) [80] regimens have also shown acceptable toxicities and similar efficacies to studies with standard doses in two Chinese phase II trials in elderly patients. Furthermore, a randomised, phase III, Korean study in elderly patients ≥70 years showed CAPOX to be superior to capecitabine alone in terms of PFS and a Japanese trial showed S-1 and oxaliplatin (SOX) to be superior to S-1 and cisplatin in terms of PFS and OS in elderly patients ≥70 years of age [81, 82].

The fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) combination regimen developed in Europe [54] was not superior to fluorouracil, leucovorin, oxaliplatin (FLO) in patients with mGC or in those patients aged ≥70 years [83] or to FOLFOX in a Chinese trial in patients aged ≥65 years [68], and its use has not been developed in Asia.

Recommendation 6: second- and further-line treatment

6a. *Second-line chemotherapy with a taxane (docetaxel, paclitaxel), or irinotecan, or ramucirumab as a single agent or in combination with paclitaxel is recommended for patients who are of PS 0–1 [A = 100% and I, A].*

6b. *Similar efficacy has been demonstrated for weekly paclitaxel and irinotecan.* This recommendation was to be removed and be replaced with the new revised 'recommendation 6b' below.

6b. *In patients* ***treated with chemotherapy which stopped before progression and who have not progressed within*** *3 months it may be appropriate to consider* ***the reintroduction of*** *the same drug combination* ***as long as any toxicity issues have been resolved*** *[A = 100% and IV, C].*

6c. ***Nivolumab, pembrolizumab or trifluridine/tipiracil (FTD/TPI, TAS-102) should be considered as third- or further-line treatment, if approved. Irinotecan or a taxane (if not used in the earlier lines) are also options for third- or further-line treatment [A = 100% and V, C]. Apatinib may also be considered but only in China [A = 100% and I, A].***

6d. *In patients with symptomatic locally advanced or recurrent disease, hypofractionated radiotherapy is an effective and well-tolerated treatment modality that may palliate bleeding, obstructive symptoms or pain [A = 100% and III, B].*

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendation 6a' and the deletion of 'recommendation 6b', with the proposal that patients with mGC who have progressed on first-line treatment are assigned to second-line treatment and care according to the treatment options presented in Figure 1. These options are based on the observations that irinotecan or docetaxel monotherapy have been shown to be superior to BSC in individual trials in both Western and Asian patients [84–87], and also in a meta-analysis [88]. A randomised phase III trial directly comparing irinotecan and paclitaxel as second-line therapy in patients with advanced GC showed them to have similar efficacy [89]. Whilst, nab-paclitaxel (not approved for GC except for Japan) has been shown to be non-inferior to paclitaxel in an open-label, randomised phase III trial [90]. However, paclitaxel plus ramucirumab is now the preferred second-line treatment option for patients with mGC and an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1, based on the results of the phase III RAINBOW trial conducted across 27 countries worldwide [91, 92], in which ~35% of the patients were of Asian ethnicity [93] (ESMO MCBS 2). A Japanese study has also investigated nab-paclitaxel and ramucirumab in a single-arm phase II trial and reported promising activity [94]. Ramucirumab monotherapy is also one of the second-line options (Figure 1) based on the results of the randomised phase III REGARD trial in which ~16% of the patients were of Asian ethnicity [95] (ESMO MCBS 1). Today, irinotecan [86, 87] or taxane monotherapy [84, 86, 90] is considered an alternative second-line treatment option for patients with mGC who are not candidates for ramucirumab treatment or where ramucirumab is not available. The experts agreed completely [A = 100%] with the new revised 'recommendation 6b' that for patients treated with chemotherapy which was stopped before progression and who have not progressed within 3 months it may be appropriate to consider the reintroduction of the same drug combination.

The experts also accepted completely the new 'recommendation 6c' [A = 100%]. Docetaxel and irinotecan have also been shown to be effective as salvage therapies [85]. Thus, for patients with disease progression after second-line therapy with a taxane +/−ramucirumab, irinotecan therapy is an option. Nivolumab, a monoclonal antibody that binds to the PD-1 receptor, is also recommended as monotherapy for treatment in the third- or later-line settings based on the results of the ATTRACTION-2 trial in mGC ECOG PS 0-1 patients, who were refractory or intolerant to two or more previous lines of chemotherapy, conducted in Japan, Korea and Taiwan [96] [not approved by the European Medicines Agency (EMA)]. Trifluridine/tipiracil (FTD/TPI, TAS-102) has demonstrated efficacy with an acceptable toxicity profile in a Japanese phase II study in patients with advanced pre-treated GC [97]. More recently, FTD/TPI was shown to produce a 31% reduction in the risk of death compared with placebo in patients with heavily pre-treated advanced or mGC in the multinational, phase III TAGS trial [98] (not approved by the EMA). In a Chinese phase III trial, apatinib, a vascular endothelial growth factor receptor 2 tyrosine kinase inhibitor, showed a significant survival benefit over placebo in the third- and later-line settings [99] and is approved for use in China. Monotherapy with pembrolizumab, another monoclonal antibody that binds to the PD-1 receptor, has shown promising activity and manageable safety in a global, single-arm phase II trial (KEYNOTE-059) in patients with advanced GEJ cancer or GC who had previously received at least two lines of prior systemic therapy [100]. This led to the United States Federal Drug Administration (FDA) approving pembrolizumab for the treatment of mGC that expresses PD-L1 [combined positive score (CPS) ≥1] and has progressed on or after two or more previous lines of therapy including platinum- and fluoropyrimidine-containing chemotherapy (not approved by the EMA). Pembrolizumab did not significantly improve OS compared with paclitaxel as second-line therapy for mGC with PD-L1 (CPS ≥1) in the phase III trial (KEYNOTE-061) [37]. Subgroup analyses suggest that the treatment effect of pembrolizumab might be more pronounced in patients with a better PS, and tumours with greater levels of PD-L1 expression, and MSI [37], all of which will be evaluated in ongoing trials in the first-line setting.

Finally, palliative radiotherapy may be an option for patients with symptomatic, locally advanced or recurrent disease [101–107]. Consistent with this, all 12 Asian experts completely accepted [A = 100%] 'recommendation 6d'.

Recommendation 7: personalised medicine and targeted therapy

7. Trastuzumab is recommended in conjunction with platinum- and fluoropyrimidine-based chemotherapy for patients with HER2-positive advanced GC [A = 100% and I, A].

The Asian experts accepted this 'recommendation' completely [A = 100%] consistent with 'recommendation 1a' above, and based on the data from the ToGA trial [22–24], a Chinese randomised controlled trial [25], several Japanese phase II trials [26, 108, 109] and one Korean trial [110]. A Japanese phase II trial has shown high antitumour activity and manageable toxicity for trastuzumab plus S-1 in elderly patients [111]. A non-randomised Japanese trial has also shown trastuzumab combined with paclitaxel to be well tolerated with promising activity, in the second- or later-line treatment of trastuzumab-naïve patients [112]. However, trastuzumab beyond progression second-line in patients who were previously treated with trastuzumab failed to improve PFS in the Japanese WJOG 7112G trial [113].

As stated previously in 'recommendation 3' above, four principal GC subtypes have been identified [44–47]. Each molecular subtype is enriched for selected molecular abnormalities [18], which include enriched copy numbers of key receptor tyrosine kinase genes, such as those for HER2, epidermal growth factor receptor (EGFR), fibroblast growth factor receptor-2 and hepatocyte growth factor (HGF) receptor (MET) or MSI-high/dMMR. These findings have potentially important implications for the development of targeted therapeutic (personalised medicine) approaches in the treatment of patients with mGC. As mentioned previously (recommendation 1) gastric tumours may be optionally tested for MSI and dMMR with a view to predicting the clinical benefit of ICIs. For example, the previously treated MSI-high advanced cancer patients in the KEYNOTE-164 and KEYNOTE 158 trials [114, 115], and the gastric and GEJ patients in the KEYNOTE-061 trial [116], showed high response rates to pembrolizumab. Therefore where nivolumab and FTD/TPI are available as 3rd-line therapies, for patients with MSI-high tumours, nivolumab would be the preferred option (Figure 1).

Indeed, PD-L1, TMB and EBV may be considered as potential biomarkers for the use of ICIs in the future [34–37]. PD-L1 in particular has been investigated as a biomarker for ICIs such as pembrolizumab and nivolumab, monoclonal antibodies that bind to the PD-1 receptor. However, the phase III KEYNOTE-061 study of pembrolizumab versus paclitaxel in patients with CPS $\geq$1 advanced GC or cancer of the GEJ (mentioned previously under 'recommendation 6' and in relation to MSI above) [37], failed to meet its primary end point and has to be considered as a negative trial, and as a result pembrolizumab is not recommended for the treatment of patients with mGC in this treatment setting. Whilst, nivolumab in a randomised placebo-controlled, phase III trial (ATTRACTION-02) [96], in Asian patients with advanced GC or cancer of the GEJ who had previously received at least two lines of prior systemic therapy, showed a statistically significant benefit in OS ($P < 0.0001$) compared with placebo regardless of PD-L1 expression. At the present time, none of the ICIs have been approved by the EMA for GC. Randomised phase III trials of anti-EGFR and anti-MET/HGF therapies have not been able to demonstrate an improvement in OS [117–120].

Recommendation 8: specific situations

8a. Metastasectomy: Gastrectomy in patients with limited metastatic disease does not improve survival [1A], was revised to read ***Gastrectomy in patients with stage IV disease or metastasectomy are not routinely recommended [A = 100% and I, A].***

8b. Peritoneal metastases: In patients with peritoneal metastases, the use of cytoreductive surgery (CRS) plus HIPEC has been studied, but this approach cannot yet be recommended outside the context of clinical research [A = 100% and IV C].

The Asian experts accepted completely [A = 100%] 'recommendation 8a' once it had been reworded. This was based on evidence in Asian patients from the randomised REGATTA trial which showed that gastrectomy in patients with limited metastatic disease does not improve survival [I, A] [121].

Also, although there have been several studies of hyperthermic intraperitoneal chemotherapy (HIPEC) in Asia, including some indicating a survival advantage, the evidence is insufficient to recommend the incorporation of HIPEC into standard therapy [122–126]. The results of randomised trials of adjuvant HIPEC from Western centres are awaited. A study which retrospectively examined the outcomes of 277 patients who were treated with CRS plus HIPEC or CRS alone suggested a survival benefit in those patients treated with HIPEC. However, the fact the study was retrospective means it could potentially be biased [127]. The experts accepted completely [A = 100%] 'recommendation 8b'.

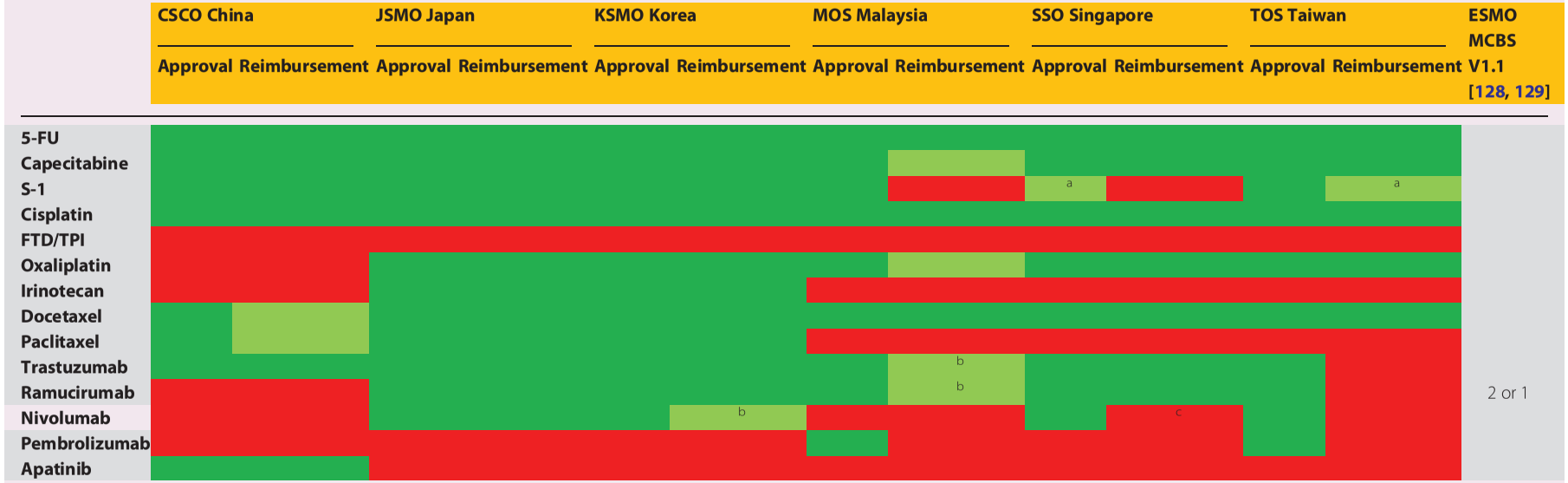
Discussion

Conclusions

The results of the voting by the Asian experts both before and after the face-to-face meeting in Kobe showed high concordance (supplementary Tables S1 and S2, available at *Annals of Oncology* online) with the ESMO recommendations for the treatment of patients with mGC published as part of the 2016 ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up for GC [18]. In terms of level of agreement there were no votes of less than an A (accept completely) following the face-to-face discussions, except for 'recommendation 4a-2'.

Thus, these guidelines can be considered to be consensus guidelines for the treatment of patients with mGC in Asia, with $\geq$80% of experts voting to accept completely or accept with reservation a specific recommendation. 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 2018, is presented for each participating country

Table 3. Summary of drug approvals and reimbursement according to Asian country



[a]Adjuvant only.
[b]Partially reimbursed in Ministry of Health hospitals and paid in full by patients in other hospitals.
[c]Nivolumab not yet approved but available.

Approved or reimbursed.

Partially approved/reimbursed or with restriction.

Not approved or reimbursed.

5-FU, 5-fluorouracil; MCBS, Magnitude of Clinical Benefit Scale; S-1, tegafur/gimeracil/oteracil; FTD/TPI, trifluridine/tipiracil.

in Table 3 and will obviously impact on some of the treatment strategies that can be adopted by certain countries.

Acknowledgements

The authors would like to thank Ms C. Tada from the secretariat of JSMO and Ms K. Marinoni, ESMO Assistant, for their preparation and on-site assistance and support during the face-to-face meeting of experts in Kobe. Dr A. Kinsella, Cancer Communications and Consultancy Ltd, Knutsford, Cheshire, UK is acknowledged for her assistance in the preparation of the manuscript funded by JSMO.

Funding

All costs relating to this consensus conference were covered by the JSMO central dedicated funds. There was no external funding of the event or the manuscript production.

Disclosure

DA reports fees for consultancy from Bayer, Merck Serono, Roche, Servier, Sanofi and BMS. EB reports fees for consultancy from Takeda, Taiho, Yakult, Esai, Eli Lilly, Chugai, Dainihon-Sumitomo, Kyowahakko-Kirin, Daiichi-Sankyo, Sanofi, Merck Serono, Ono, Bristle-Myers Squibb, and Astellas; and research funding from Takeda, Taiho, Yakult, Esai, Eli Lilly, Chugai, Kyowahakko-Kirin, Daiichi-Sankyo, Merck Serono, Ono, Bristle-Myers Squibb, Astellas, Shionogi, Bayer, MSD, and Linical. BCC reports fees for consultancy from Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, BMS, Yuhan, Pfizer, Eli Lilly and Janssen, and research funding from Novartis, Bayer, AstraZeneca, MOGAM Institute, Don-A ST, Champions Oncology and Janssen. LTC reports fees for consultancy from ONO, BMS, MSD, Eli Lilly, PhamaEngine, Five Prime, Novartis and AstraZeneca; remuneration from ONO, BMS, MSD, Eli Lilly, PhamaEngine, TTY, SyncoreBio, Five Prime, Novartis, Astra Zeneca, Ipsen; research funding from Novartis, Pfizer, Merck Serono, Polaris, TTY, SyncoreBio, Celgene, BMS; and patent royalties/licensing fees from HuniLife; and is a board member of ScinoPharm Taiwan, Ltd. HK reports research funding from Chugai, Eisai, and Daiichi-Sankyo. KK reports fees for consultancy from MSD, ONO Pharmaceuticals, Beigene, and Oncolys biopharma; and research funding from MSD, Ono Pharmaceuticals, Shionogi, and Beigene. FL reports fees for consultancy from Lilly, Merck Sharp & Dohme, Bristol-Myers Squibb, and Astellas Pharma; honoraria from Lilly, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Elsevier, BioNTech AG, SERVIER, Infomedica, Merck KGaA, and Roche; research funding from Bristol-Myers Squibb, and fees for travel, accommodation and expenses from Bristol-Myers Squibb. EM is an advisor for Amgen, Bayer, Sanofi, Servier and Roche. HM reports consultancy fees for Bayer, Boehringer-Ingelheim, BMS, Celgene, Chugai, Daiichi-Sankyo, Dainihon-Sumitomo, Eisai, Janssen, Kowa, Kyowa-Kirin, Lilly, Merck-Serono, MSD, Novartis, Ono, Ohtsuka, Pfizer, Sanofi, Shire Japan, Taiho and Takeda and research funding from Asahi Kasei Pharma, Astellas, Bayer, Boehringer-Ingelheim, BMS, Chugai, Daiichi-Sankyo, Dainihon-Sumitomo, Eisai, Kyowa-Kirin, Lilly, MSD, Nihon Shiyaku, Novartis, Ono, Pfizer, Sanofi, Taiho, Taisho-Toyama, Takeda, Teijin Pharma and Yakult. KM reports fees for consultancy from Chugai, Eli Lilly, Takeda, Ono, Bayer, and Taiho; and research funding from Gilead Sciences, Merck Serono, Ono, Pfizer, Kyowa Hakko Kirin, Shionogi, Daiichi-Sankyo, and MSD. MN reports fees for consultancy from MSD Oncology, Singapore; and honoraria for talks from Taiho Pharmaceuticals May 2018, and MSD Oncology November 2019. TN reports fees for consultancy from Taiho Pharm., Sanofi, Chugai Pharm, Takeda Pharm, Sawai Pharm, Bayer, Bristol-Myers Squibb, Merck Serono, Ono Pharm, and Mochida Pharm; and research funding from Taiho Pharm., Chugai Pharm, Takeda Pharm, Sanofi, Merck Serono, Daiichi-Sankyo, Ono Pharm, MSD and Esai. MHR reports fees for consultancy from Novartis, Lilly, MSD, Bristol-Myers-Squibb, ONO, Taiho and DAEHWA pharm. ECS reports fees for consultancy from BMS, Servier, Celgene, Five Prime Therapeutics, and Gritstone Oncology. KS reports fees for consultancy from Astellas Pharma, Lilly, Bristol-Myers Squibb, Takeda, Pfizer and Ono Pharmaceutical; and research funding from Dainippon Sumitomo Pharma, Lilly, MSD, Daiichi-Sankyo, Taiho Pharmaceutical, Chugai Pharma, and Ono Pharmaceutical. JT reports fees for consultancy from Bayer, Boehringer-Ingelheim, Chugai, Genentech Inc., Ipsen, Lilly, MSD, Merck Serono, Merrimack, Merus, Novartis, Peptomyc, Pfizer, Rafael Pharmaceuticals, F. Hoffmann-La Roche Ltd, Sanofi, Seattle Genetics, Symphogen and Taiho. EVC reports fees for consultancy from Bayer, BMS, Celgene, Lilly, Merck KGaA, Novartis and Servier, and research funding from Amgen, Bayer, BMS, Celgene, Ipsen, Lilly, Merck, Merck KGaA, Novartis, Roche and Servier. WZWI reports fees for consultancy from Boehringer-Ingelheim Malaysia, ROCHE Malaysia, Eisei Malaysia, and Eli Lilly Malaysia; and research funding from Amgen Inc., ROCHE Inc. and Merck Inc. KHY reports fees for consultancy from Boehringer-Ingelheim, Takeda, Bristol-Myers-Squibb (BMS), Ono Pharmaceutical, MSD, Eli Lilly and Amgen; and honoraria from Boehringer Ingelheim, Takeda, Bristol-Myers-Squibb (BMS), Ono Pharmaceutical, MSD, Eli Lilly and Amgen. TY reports honoraria (lecture fees) from Sanofi K.K., Chugai Pharmaceutical Co., Ltd, Eli Lilly Japan K.K, and Merck Serono Co., Ltd; and grant/research funding from MSD K.K., Sanofi K.K., Sumitomo Dainippon Pharma Co., Ltd, Chugai Pharmaceutical Co., Ltd, GlaxoSmithKline K.K. and Nippon Boehringer-Ingelheim Co., Ltd. WPY reports fees for consultancy from ASLAN, MSD, BMS, and Merck. JYD, JL, ZL, IMN, YN, GP and TT have declared no conflicts of interest.

References

1. Ferlay J, Soerjomataram I, Dikshit R et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136(5): E359–E386.
2. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends—an update. Cancer Epidemiol Biomarkers Prev 2016; 25(1): 16–27.

3. Colquhoun A, Arnold M, Ferlay J et al. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. Gut 2015; 64(12): 1881–1888.
4. Karimi P, Islami F, Anandasabapathy S et al. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev 2014; 23(5): 700–713.
5. Anderson WF, Camargo MC, Fraumeni JF Jr et al. Age-specific trends in incidence of noncardia gastric cancer in US adults. JAMA 2010; 303(17): 1723–1728.
6. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer 2006; 118(12): 3030–3044.
7. Bertuccio P, Chatenoud L, Levi F et al. Recent patterns in gastric cancer: a global overview. Int J Cancer 2009; 125(3): 666–673.
8. Camargo MC, Anderson WF, King JB et al. Divergent trends for gastric cancer incidence by anatomical subsite in US adults. Gut 2011; 60(12): 1644–1649.
9. de Martel C, Forman D, Plummer M. Gastric cancer: epidemiology and risk factors. Gastroenterol Clin North Am 2013; 42(2): 219–240.
10. Steevens J, Botterweck AA, Dirx MJ et al. Trends in incidence of oesophageal and stomach cancer subtypes in Europe. Eur J Gastroenterol Hepatol 2010; 22(6): 669–678.
11. Fock KM, Talley N, Moayyedi P et al. Asia-Pacific consensus guidelines on gastric cancer prevention. J Gastroenterol Hepatol 2008; 23(3): 351–365.
12. Japanese Gastric Cancer A. Japanese gastric cancer treatment guidelines 2014 (ver. 4.). Gastric Cancer 2017; 20: 1–19.
13. Jun JK, Choi KS, Lee H-Y et al. Effectiveness of the Korean National Cancer Screening Program in reducing gastric cancer mortality. Gastroenterology 2017; 152(6): 1319–1328. e1317.
14. Lee JH, Kim JG, Jung HK et al. [Synopsis on clinical practice guideline of gastric cancer in Korea: and evidence-based approach]. Korean J Gastroenterol 2014; 63(2): 66–81.
15. Lee JH, Kim JG, Jung HK et al. Clinical practice guidelines for gastric cancer in Korea: an evidence-based approach. J Gastric Cancer 2014; 14(2): 87–104.
16. Park HA, Nam SY, Lee SK et al. The Korean guideline for gastric cancer screening. J Korean Med Assoc 2015; 58(5): 373–384.
17. Shen L, Shan YS, Hu HM et al. Management of gastric cancer in Asia: resource-stratified guidelines. Lancet Oncol 2013; 14(12): e535–e547.
18. Smyth EC, Verheij M, Allum W et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016; 27(Suppl 5): v38–v49.
19. Muro K, Lordick F. Tsushima T et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic oesophageal cancer: a JSMO–ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS. Ann Oncol 2019; 30(1): 34–43.
20. Yoshino T, Arnold D, Taniguchi H et al. 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. Ann Oncol 2018; 29(1): 44–70.
21. Dykewicz CA. Centers for Disease Control and Prevention, Infectious Diseases Society of America, American Society of Blood and Marrow Transplantation. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33(2): 139–144.
22. Bang YJ, Van Cutsem E, Feyereislova A et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010; 376(9742): 687–697.
23. Van Cutsem E, Bang YJ, Feng-Yi F et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. Gastric Cancer 2015; 18(3): 476–484.
24. Sawaki A, Ohashi Y, Omuro Y et al. Efficacy of trastuzumab in Japanese patients with HER2-positive advanced gastric or gastroesophageal junction cancer: a subgroup analysis of the Trastuzumab for Gastric Cancer (ToGA) study. Gastric Cancer 2012; 15(3): 313–322.
25. Shen L, Xu JM, Feng FY et al. [Trastuzumab in combination with chemotherapy versus chemotherapy alone for first-line treatment of HER2-positive advanced gastric or gastroesophageal junction cancer: a phase III, multi-center, randomized controlled trial, Chinese subreport]. Zhonghua Zhong Liu Za Zhi 2013; 35: 295–300.
26. Kurokawa Y, Sugimoto N, Miwa H et al. Phase II study of trastuzumab in combination with S-1 plus cisplatin in HER2-positive gastric cancer (HERBIS-1). Br J Cancer 2014; 110(5): 1163–1168.
27. Marsh S, Hoskins JM. Irinotecan pharmacogenomics. Pharmacogenomics 2010; 11(7): 1003–1010.
28. Okuyama Y, Hazama S, Nozawa H et al. Prospective phase II study of FOLFIRI for mCRC in Japan, including the analysis of UGT1A1 28/6 polymorphisms. Jpn J Clin Oncol 2011; 41(4): 477–482.
29. Satoh T, Ura T, Yamada Y et al. Genotype-directed, dose-finding study of irinotecan in cancer patients with UGT1A1*28 and/or UGT1A1*6 polymorphisms. Cancer Sci 2011; 102(10): 1868–1873.
30. Cheng L, Li M, Hu J et al. UGT1A1*6 polymorphisms are correlated with irinotecan-induced toxicity: a system review and meta-analysis in Asians. Cancer Chemother Pharmacol 2014; 73(3): 551–560.
31. Akiyama Y, Fujita K, Nagashima F et al. Genetic testing for UGT1A1*28 and *6 in Japanese patients who receive irinotecan chemotherapy. Ann Oncol 2008; 19(12): 2089–2090.
32. Ando Y, Saka H, Ando M et al. Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res 2000; 60(24): 6921–6926.
33. Le DT, Uram JN, Wang H et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015; 372(26): 2509–2520.
34. Ammannagari N, Atasoy A. Current status of immunotherapy and immune biomarkers in gastro-esophageal cancers. J Gastrointest Oncol 2018; 9(1): 196–207.
35. Sidaway P. Immunotherapy-responsive gastric cancers identified. Nat Rev Clin Oncol 2018 Jul 30 [Epub ahead of print], doi: 10.1038/s41571-018-0079y.
36. Kim ST, Cristescu R, Bass AJ et al. Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. Nat Med 2018; 24(9): 1449–58.
37. Shitara K, Özgüroğlu M, Bang Y-J et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet 2018; 392(10142): 123–133.
38. van der Post RS, Vogelaar IP, Carneiro F et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. J Med Genet 2015; 52(6): 361–374.
39. Yabuta T, Shinmura K, Tani M et al. E-cadherin gene variants in gastric cancer families whose probands are diagnosed with diffuse gastric cancer. Int J Cancer 2002; 101(5): 434–441.
40. Yamada H, Shinmura K, Ito H et al. Germline alterations in the CDH1 gene in familial gastric cancer in the Japanese population. Cancer Sci 2011; 102(10): 1782–1788.
41. Yamada M, Fukagawa T, Nakajima T et al. Hereditary diffuse gastric cancer in a Japanese family with a large deletion involving CDH1. Gastric Cancer 2014; 17(4): 750–756.
42. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. an attempt at a histo-clinical classification. Acta Pathol Microbiol Scand 1965; 64: 31–49.
43. Association JGC. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011; 14: 101–112.
44. Cancer GARN. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014; 513: 202–209.
45. Liu Y, Sethi NS, Hinoue T et al. Comparative molecular analysis of gastrointestinal adenocarcinomas. Cancer Cell 2018; 33(4): 721–735. e728.
46. Ichikawa H, Nagahashi M, Shimada Y et al. Actionable gene-based classification toward precision medicine in gastric cancer. Genome Med 2017; 9: 93.

47. Cristescu R, Lee J, Nebozhyn M et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat Med 2015; 21(5): 449–456.
48. Lei Z, Tan IB, Das K et al. Identification of molecular subtypes of gastric cancer with different responses to PI3-kinase inhibitors and 5-fluorouracil. Gastroenterology 2013; 145(3): 554–565.
49. Bouche O, Raoul JL, Bonnetain F et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study–FFCD 9803. J Clin Oncol 2004; 22: 4319–4328.
50. Glimelius B, Ekstrom K, Hoffman K et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol 1997; 8(2): 163–168.
51. Wagner AD, Unverzagt S, Grothe W et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2010; CD004064.
52. Kim NK, Park YS, Heo DS et al. A phase III randomized study of 5-fluorouracil and cisplatin versus 5-fluorouracil, doxorubicin, and mitomycin C versus 5-fluorouracil alone in the treatment of advanced gastric cancer. Cancer 1993; 71(12): 3813–3818.
53. Koizumi W, Narahara H, Hara T et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 2008; 9(3): 215–221.
54. Al-Batran SE, Hartmann JT, Hofheinz R et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2008; 19(11): 1882–1887.
55. Cunningham D, Starling N, Rao S et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358(1): 36–46.
56. Ryu M-H, Park YI, Chung I-J et al. Phase III trial of s-1 plus oxaliplatin (SOX) vs s-1 plus cisplatin (SP) combination chemotherapy for first-line treatment of advanced gastric cancer (AGC): SOPP study. J Clin Oncol 2016; 34 (Suppl 15); 4015–4015.
57. Yamada Y, Higuchi K, Nishikawa K et al. Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naive patients with advanced gastric cancer. Ann Oncol 2015; 26(1): 141–148.
58. Kang YK, Kang WK, Shin DB et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol 2009; 20(4): 666–673.
59. Okines AF, Norman AR, McCloud P et al. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Ann Oncol 2009; 20(9): 1529–1534.
60. Yamaguchi K, Sawaki A, Doi T et al. Efficacy and safety of capecitabine plus cisplatin in Japanese patients with advanced or metastatic gastric cancer: subset analyses of the AVAGAST study and the ToGA study. Gastric Cancer 2013; 16(2): 175–182.
61. Ter Veer E, Ngai LL, Valkenhoef GV et al. Capecitabine, 5-fluorouracil and S-1 based regimens for previously untreated advanced oesophagogastric cancer: a network meta-analysis. Sci Rep 2017; 7: 7142.
62. Lee JL, Kang YK, Kang HJ et al. A randomised multicentre phase II trial of capecitabine vs S-1 as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. Br J Cancer 2008; 99(4): 584–590.
63. Kim GM, Jeung HC, Rha SY et al. A randomized phase II trial of S-1-oxaliplatin versus capecitabine-oxaliplatin in advanced gastric cancer. Eur J Cancer 2012; 48(4): 518–526.
64. Van Cutsem E, Moiseyenko VM, Tjulandin S et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006; 24(31): 4991–4997.
65. Shah MA, Janjigian YY, Stoller R et al. Randomized multicenter phase II study of modified docetaxel, cisplatin, and fluorouracil (DCF) versus DCF plus growth factor support in patients with metastatic gastric adenocarcinoma: a study of the US Gastric Cancer Consortium. J Clin Oncol 2015; 33(33): 3874–3879.
66. Yamada Y, Boku N, Mizusawa J et al. Phase III study comparing triplet chemotherapy with S-1 and cisplatin plus docetaxel versus doublet chemotherapy with S-1 and cisplatin for advanced gastric cancer. J Clin Oncol 2018; 36(Suppl); Abstr 4009.
67. Liang R, Chen X-Y, Lin Y et al. Clinical efficacy and safety of standard versus modified DCF regimens in treatment of advanced gastric cancer. Int J Exp Med 2016; 9: 9404–9410.
68. Liu M, Hu G, Wang Y et al. Comparison of FOLFOX and DOF regimens as first-line treatment in East Asian patients with advanced gastric cancer. Onco Targets Ther 2018; 11: 375–381.
69. Yun J, Lee J, Park SH et al. A randomised phase II study of combination chemotherapy with epirubicin, cisplatin and capecitabine (ECX) or cisplatin and capecitabine (CX) in advanced gastric cancer. Eur J Cancer 2010; 46(5): 885–891.
70. Koizumi W, Kim YH, Fujii M et al. Addition of docetaxel to S-1 without platinum prolongs survival of patients with advanced gastric cancer: a randomized study (START). J Cancer Res Clin Oncol 2014; 140(2): 319–328.
71. Lu Z, Zhang X, Liu W et al. A multicenter, randomized trial comparing efficacy and safety of paclitaxel/capecitabine and cisplatin/capecitabine in advanced gastric cancer. Gastric Cancer 2018;
72. Dank M, Zaluski J, Barone C et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol 2008; 19(8): 1450–1457.
73. Guimbaud R, Louvet C, Ries P et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French intergroup (Federation Francophone de Cancerologie Digestive, Federation Nationale des Centres de Lutte Contre le Cancer, and Groupe Cooperateur Multidisciplinaire en Oncologie) study. J Clin Oncol 2014; 32: 3520–3526.
74. Koizumi W, Akiya T, Sato A et al. Phase II study of S-1 as first-line treatment for elderly patients over 75 years of age with advanced gastric cancer: the Tokyo Cooperative Oncology Group study. Cancer Chemother Pharmacol 2010; 65(6): 1093–1099.
75. Nishikawa K, Yoshino S, Morita S et al. Safety and efficacy of S-1 treatment in elderly patients with advanced recurrent gastric cancer: a subgroup analysis from the phase III JFMC36-0701 trial. Annals Oncol 2017; 28: 679P.
76. Hsu CH, Yeh KH, Chen LT et al. Weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin in the treatment of advanced gastric cancers. an effective and low-toxic regimen for patients with poor general condition. Oncology 1997; 54(4): 275–280.
77. Yeh KH, Cheng AL, Lin MT et al. A phase II study of weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin (HDFL) in the treatment of recurrent or metastatic colorectal cancers. Anticancer Res 1997; 17(5B): 3867–3871.
78. Taiwan Cooperative Oncology Group. Gastric Cancer Treatment Guideline (in Chinese). Taiwan Cooperative Group. National Health Research Institutes Taipei, Taiwan 2012.
79. Xiang XJ, Zhang L, Qiu F et al. A phase II study of capecitabine plus oxaliplatin as first-line chemotherapy in elderly patients with advanced gastric cancer. Chemotherapy 2012; 58(1): 1–7.
80. Zhao JG, Qiu F, Xiong JP et al. A phase II study of modified FOLFOX as first-line chemotherapy in elderly patients with advanced gastric cancer. Anticancer Drugs 2009; 20(4): 281–286.
81. Hwang IG, Ji JH, Kang JH et al. A multi-center, open-label, randomized phase III trial of first-line chemotherapy with capecitabine monotherapy versus capecitabine plus oxaliplatin in elderly patients with advanced gastric cancer. J Geriatr Oncol 2017; 8(3): 170–175.

82. Bando H, Yamada Y, Tanabe S et al. Efficacy and safety of S-1 and oxaliplatin combination therapy in elderly patients with advanced gastric cancer. Gastric Cancer 2016; 19(3): 919–926.
83. Al-Batran SE, Pauligk C, Homann N et al. The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65+). Eur J Cancer 2013; 49(4): 835–842.
84. Ford HE, Marshall A, Bridgewater JA et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol 2014; 15(1): 78–86.
85. Kang JH, Lee SI, Lim DH et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 2012; 30(13): 1513–1518.
86. Roy AC, Park SR, Cunningham D et al. A randomized phase II study of PEP02 (MM-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma. Ann Oncol 2013; 24(6): 1567–1573.
87. Thuss-Patience PC, Kretzschmar A, Bichev D et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer–a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011; 47(15): 2306–2314.
88. Janowitz T, Thuss-Patience P, Marshall A et al. Chemotherapy vs supportive care alone for relapsed gastric, gastroesophageal junction, and oesophageal adenocarcinoma: a meta-analysis of patient-level data. Br J Cancer 2016; 114(4): 381–387.
89. Hironaka S, Ueda S, Yasui H et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol 2013; 31: 4438–4444.
90. Shitara K, Takashima A, Fujitani K et al. Nab-paclitaxel versus solvent-based paclitaxel in patients with previously treated advanced gastric cancer (ABSOLUTE): an open-label, randomised, non-inferiority, phase 3 trial. Lancet Gastroenterol Hepatol 2017; 2(4): 277–287.
91. Al-Batran SE, Van Cutsem E, Oh SC et al. Quality-of-life and performance status results from the phase III RAINBOW study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated gastric or gastroesophageal junction adenocarcinoma. Ann Oncol 2016; 27(4): 673–679.
92. Wilke H, Muro K, Van Cutsem E et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014; 15(11): 1224–1235.
93. Shitara K, Muro K, Shimada Y et al. Subgroup analyses of the safety and efficacy of ramucirumab in Japanese and Western patients in RAINBOW: a randomized clinical trial in second-line treatment of gastric cancer. Gastric Cancer 2016; 19(3): 927–938.
94. Bando H, Shimodaira H, Fujitani K et al. A phase II study of nab-paclitaxel in combination with ramucirumab in patients with previously treated advanced gastric cancer. Eur J Cancer 2018; 91: 86–91.
95. Fuchs CS, Tomasek J, Yong CJ et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014; 383(9911): 31–39.
96. Kang YK, Boku N, Satoh T et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017; 390(10111): 2461–2471.
97. Bando H, Doi T, Muro K et al. A multicenter phase II study of TAS-102 monotherapy in patients with pre-treated advanced gastric cancer (EPOC1201). Eur J Cancer 2016; 62: 46–53.
98. Shitara K, Doi T, Dvorkin M et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncology 2018; 19(11): 1437–1448.
99. Li J, Qin S, Xu J et al. Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. J Clin Oncol 2016; 34(13): 1448–1454.
100. Fuchs CS, Doi T, Jang RW et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. JAMA Oncol 2018; 4(5): e180013.
101. Asakura H, Hashimoto T, Harada H et al. Palliative radiotherapy for bleeding from advanced gastric cancer: is a schedule of 30 Gy in 10 fractions adequate? J Cancer Res Clin Oncol 2011; 137(1): 125–130.
102. Hashimoto K, Mayahara H, Takashima A et al. Palliative radiation therapy for hemorrhage of unresectable gastric cancer: a single institute experience. J Cancer Res Clin Oncol 2009; 135(8): 1117–1123.
103. Kim MM, Rana V, Janjan NA et al. Clinical benefit of palliative radiation therapy in advanced gastric cancer. Acta Oncol 2008; 47(3): 421–427.
104. Lee YH, Lee JW, Jang HS. Palliative external beam radiotherapy for the treatment of tumor bleeding in inoperable advanced gastric cancer. BMC Cancer 2017; 17: 541.
105. Tey J, Back MF, Shakespeare TP et al. The role of palliative radiation therapy in symptomatic locally advanced gastric cancer. Int J Radiat Oncol Biol Phys 2007; 67(2): 385–388.
106. Tey J, Choo BA, Leong CN et al. Clinical outcome of palliative radiotherapy for locally advanced symptomatic gastric cancer in the modern era. Medicine (Baltimore) 2014; 93(22): e118.
107. Tey J, Soon YY, Koh WY et al. Palliative radiotherapy for gastric cancer: a systematic review and meta-analysis. Oncotarget 2017; 8: 25797–25805.
108. Miura Y, Sukawa Y, Hironaka S et al. Five-weekly S-1 plus cisplatin therapy combined with trastuzumab therapy in HER2-positive gastric cancer: a phase II trial and biomarker study (WJOG7212G). Gastric Cancer 2018; 21(1): 84–95.
109. Okita A, Imai H, Takahashi M et al. Efficacy and safety of trastuzumab in combination with S-1 and cisplatin therapy for Japanese patients with HER2-positive advanced gastric cancer: retrospective analysis. Tohoku J Exp Med 2018; 245(2): 123–129.
110. Ryu MH, Yoo C, Kim JG et al. Multicenter phase II study of trastuzumab in combination with capecitabine and oxaliplatin for advanced gastric cancer. Eur J Cancer 2015; 51(4): 482–488.
111. Kimura Y, Fujii M, Masuishi T et al. Multicenter phase II study of trastuzumab plus S-1 alone in elderly patients with HER2-positive advanced gastric cancer (JACCRO GC-06). Gastric Cancer 2018; 21(3): 421–427.
112. Nishikawa K, Takahashi T, Takaishi H et al. Phase II study of the effectiveness and safety of trastuzumab and paclitaxel for taxane- and trastuzumab-naive patients with HER2-positive, previously treated, advanced, or recurrent gastric cancer (JFMC45-1102). Int J Cancer 2017; 140(1): 188–196.
113. Makiyama A, Sagara K, Kawada J et al. A randomized phase II study of weekly paclitaxel+/-trastuzumab in patients with HER2-positive advanced gastric or gastro-esophageal junction cancer refractory to trastuzumab combined with fluoropyrimidine and paltinum: wJOG7112G. J Clin Oncol 2018; 36(Suppl 15): 4011–4011.
114. Diaz LA Jr, Marabelle A, Kim TW et al. Efficacy of pembrolizumab in phase 2 KEYNOTE-164 and KEYNOT-158 studies of microsatellite instability high cancers. Annals of Oncol 2017; 28: 386P.
115. Le DY, Kavan P, Kim TW et al. KEYNOTE-164: pembrolizumab for patients with advancer microsatellite instability high (MSI-H) colorectal cancer. J Clin Oncol 2018; 36; Abstr 3514.

116. Shitara K, Ozguroglu M, Bang Y et al. KEYNOTE-061: phase 3 study of pemborlizumab vs paclitaxel for previously treated advanced gastric cancer or gastroesophageal junction(GEJ) cancer. Annals Oncol 2018; 29: LBA 005.
117. Catenacci DVT, Tebbutt NC, Davidenko I et al. Rilotumumab plus epirubicin, cisplatin, and capecitabine as first-line therapy in advanced MET-positive gastric or gastro-oesophageal junction cancer (RILOMET-1): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017; 18(11): 1467–1482.
118. Lordick F, Kang YK, Chung HC et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol 2013; 14(6): 490–499.
119. Shah MA, Bang YJ, Lordick F et al. Effect of fluorouracil, leucovorin, and oxaliplatin with or without onartuzumab in HER2-negative, MET-positive gastroesophageal adenocarcinoma: the METGastric randomized clinical trial. JAMA Oncol 2017; 3(5): 620–627.
120. Waddell T, Chau I, Cunningham D et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol 2013; 14(6): 481–489.
121. Fujitani K, Yang HK, Mizusawa J et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol 2016; 17(3): 309–318.
122. Desiderio J, Chao J, Melstrom L et al. The 30-year experience-A meta-analysis of randomised and high-quality non-randomised studies of hyperthermic intraperitoneal chemotherapy in the treatment of gastric cancer. Eur J Cancer 2017; 79: 1–14.
123. Ishigami H, Yamaguchi H, Yamashita H et al. Surgery after intraperitoneal and systemic chemotherapy for gastric cancer with peritoneal metastasis or positive peritoneal cytology findings. Gastric Cancer 2017; 20(Suppl 1): 128–134.
124. Seshadri RA, Glehen O. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in gastric cancer. WJD 2016; 22(3): 1114–1130.
125. Wu HT, Peng KW, Ji ZH et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy with lobaplatin and docetaxel to treat synchronous peritoneal carcinomatosis from gastric cancer: results from a Chinese center. Eur J Surg Oncol 2016; 42(7): 1024–1034.
126. Yang XJ, Huang CQ, Suo T et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. Ann Surg Oncol 2011; 18(6): 1575–1581.
127. Bonnot PE, Piessen G, Pocard M et al. CYTO-CHIP: cytoreductive surgery versus cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for gastric cancer with peritoneal metastasis: a propensity score analysis from BIG, RENAPE and FREGAT working groups. J Clin Oncol 2018; 36; Abstr 8.
128. Cherny NI, Dafni U, Bogaerts J et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol 2017; 28(10): 2340–2366.
129. Dafni U, Karlis D, Pedeli X et al. Detailed statistical assessment of the characteristics of the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) threshold rules. ESMO Open 2017; 2(4): e000216.