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SPECIAL ARTICLE

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

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The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with gastric cancer (GC), published in late 2022 and the updated ESMO Gastric Cancer Living Guideline published in July 2023, were adapted in August 2023, according to previously established standard methodology, to produce the Pan-Asian adapted (PAGA) ESMO consensus guidelines for the management of Asian patients with GC. The adapted guidelines presented in this manuscript represent the consensus opinions reached by a panel of Asian experts in the treatment of patients with GC representing the oncological societies of China (CSCO), Indonesia (ISHMO), India (ISMPO), Japan (JSMO), Korea (KSMO), Malaysia (MOS), the Philippines (PSMO), Singapore (SSO), Taiwan (TOS) and Thailand (TSCO), coordinated by ESMO and the Japanese Society of Medical Oncology (JSMO). The voting was based on scientific evidence and was independent of the current treatment practices, drug access restrictions and reimbursement decisions in the different Asian regions represented by the 10 oncological societies. The latter are discussed separately in the manuscript. The aim is to provide guidance for the optimisation and harmonisation of the management of patients with GC across the different regions of Asia, drawing on the evidence provided by both Western and Asian trials, whilst respecting the differences in screening practices, molecular profiling and age and stage at presentation. Attention is drawn to the disparity in the drug approvals and reimbursement strategies, between the different regions of Asia.

Key words: ESMO, guidelines, Pan-Asian, gastric cancer, treatment

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INTRODUCTION

With over a million estimated new cases globally in 2020, gastric cancer (GC) is the sixth most common cancer (5.6% of all new cases) and the third highest cause of cancer death (7.7% of all cancer deaths).[1] Both the incidence of and deaths from GC were almost twice as high for men as for women,[1] and East Asia accounts for over half of all GC cases worldwide.[1,2]

Based on the site/location of the tumour, GC is classified as either proximal GC [including the cardia and oesophagogastric junction (OGJ)] or distal GC (of the antrum/pylorus), which have different aetiologies. Proximal GC is associated with oesophageal reflux and obesity and is more common in Western countries; Epstein-Barr virus-positive GC is more common in the upper part and body of the stomach and has a similar prevalence in Asia to elsewhere. Distal GC is principally associated with chronic *Helicobacter pylori* infection. Globally, the incidence of distal gastric adenocarcinoma is twice that of proximal gastric adenocarcinoma,[3] although this ratio does vary between and within countries. Also, an increase in the incidence of proximal OGJ cancers has been reported in Japan.[4]

As for GC as a whole, the highest rates for both subtypes are seen in Eastern/Southeastern Asia.[3] *Helicobacter pylori* infection, dietary and lifestyle factors[5] as well as genetics[6,7] are all thought to play a role in GC development. *Helicobacter pylori* infection is a major factor in distal GC development.[8] In China, a case-cohort study showed that 78.5% of distal and 62.1% of proximal GC cases could be attributed to *H. pylori* infection.[9] Also, a meta-analysis revealed that the prevalence of *H. pylori* in distal GC cases in China was 66.5% (ranging from 53.1% in Northern China to 78.9% in Northwest China), based on the pooled data from 55 studies.[10] Meanwhile, in Malaysia, ∼70% of GC cases were shown to be distal GC,[11] except for one small study,[12] which showed proximal GC to be the prevalent subtype, seen in 14/23 (61%) patients, from a region of northeastern Malaysia reported to have one of the lowest rates of *H. pylori* infection in the world and an exceptionally low incidence of GC. A systematic review and meta-analysis also found an association between proximal GC and *H. pylori* infection for East Asia with a population attributable fraction of 60.7%.[13] The role played by *H. pylori* infection is further highlighted by a Taiwanese study where a population-based eradication of *H. pylori* resulted in a reduction in the incidence of GC by 53% between 2004 and 2016.[14] Also, a meta-analysis of data from six randomised trials, five of which were conducted in Asian populations, of healthy and asymptomatic individuals who tested positive for *H. pylori*, found that *H. pylori* eradication therapy reduced the risk of developing GC by a third.[15] For regions with a high incidence of GC, a recent global consensus meeting in Taipei agreed that a screen-and-treat strategy for *H. pylori* infection in young adults should be recommended.[16]

The most recent European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with GC were published in 2022[5] with the ESMO Gastric Cancer Living Guideline, v1.1 published in July 2023 (https://www.esmo.org/living-guidelines/esmo-gastric-cancer-living-guideline).[17] Therefore, a decision was taken by ESMO and the Japanese Society of Medical Oncology (JSMO) that these latest ESMO guidelines should be adapted to provide updated Pan-Asian guidelines for the management and treatment of GC in patients of Asian ethnicity. This manuscript summarises the Pan-Asian adapted guidelines developed and agreed at a face-to-face working meeting that took place in Tokyo on 26 August 2023, hosted by JSMO. Each recommendation is accompanied by the level of evidence, grade of recommendation (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.102226) and the percentage consensus reached, together with the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) and ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) scores as appropriate.

METHODOLOGY

This Pan-Asian adaptation of the current ESMO Clinical Practice Guidelines,[5] and associated updates,[17] was prepared in accordance with the principles of ESMO standard operating procedures (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology) and was a JSMO-ESMO initiative endorsed by the Chinese Society of Clinical Oncology (CSCO), the Indonesian Society of Hematology and Medical Oncology (ISHMO), the Indian Society of Medical and Paediatric Oncology (ISMPO), the Korean Society of Medical Oncology (KSMO), the Malaysian Oncological Society (MOS), the Philippine Society of Medical Oncology (PSMO), the Singapore Society of Oncology (SSO), the Taiwan Oncology Society (TOS) and the Thai Society of Clinical Oncology (TSCO). An international panel of experts was selected from the JSMO ($n = 7$), the ESMO ($n = 5$) and two experts from each of the nine other oncological societies. Only two of the seven expert members from the JSMO (HK and YN) were allowed to vote on the

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

Recommendations	Acceptability consensus
1: Epidemiology	
1a. If a familial cancer syndrome is suspected, referral to a geneticist for assessment is recommended [V, A].	100%
1b. Population-based endoscopic screening of asymptomatic individuals is only recommended in regions with a very high incidence of gastric cancer [V, B].	100%
2: Diagnosis, pathology and molecular biology	
2a. Diagnosis should be made from multiple (5-8) endoscopic biopsies to guarantee an adequate representation of the tumour [IV, B].	100%
2b. The histological diagnosis should be reported according to WHO criteria [V, B].	100%
2c. HER2 expression by IHC and/or amplification by *in situ* hybridisation [I, A; ESCAT score: I-A], PD-L1 by IHC according to CPS [I, A] and MSI-H/dMMR [II, A; ESCAT score: I-B] are validated predictive biomarkers. Claudin 18.2 expression by IHC [I, A; ESCAT score: I-A] may be examined, if available.	100%
3: Staging	
3a. Initial staging and risk assessment should include physical examination, full and differential blood count, liver and renal function tests, **upper gastrointestinal** endoscopy and a contrast-enhanced CT scan of the thorax **and whole** abdomen **including the** pelvis [V, A].	100%
3b. FDG—PET—CT is not routinely recommended [III, C].	100%
3c.	
3c-i. **Upfront surgery**: Diagnostic laparoscopy and peritoneal washings for cytology **should be considered** for **selected** patients with resectable gastric cancer **[III, B].**	**100%**
3c-ii. **Perioperative ChT:** Diagnostic laparoscopy and peritoneal washings for cytology are recommended for patients with resectable gastric cancer who are candidates for perioperative ChT [III, B].	**100%**
3d. The TNM stage should be recorded according to the 8th edition of the AJCC/UICC staging manual [ref] [IV, A].	100%
4: Localised gastric cancer	
4a. Multidisciplinary treatment planning before any treatment decision is mandatory [IV, B].	100%
4b. Endoscopic or surgical resection alone is appropriate for selected very early tumours (stage IA) [III, B].	100%
4c. Patients should undergo D2 resection in a high-volume surgical centre [II, B].	100%
5: Perioperative chemotherapy	
5a. Peri-operative (pre- and post-operative) chemotherapy **should be considered** for **selected** patients with stage >IB resectable gastric cancer [I, A].	**100%**
5b. **Doublet/triplet ChT regimens are recommended [II, A].**	**100%**
5c. **For patients who are candidates for a triplet ChT regimen, FLOT [ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: A] or DOS [ESMO-MCBS v1.1 score: A] are recommended [II, A].**	**100%**
5d. For patients **who are candidates** for **doublet perioperative** chemotherapy, a combination of a fluoropyrimidine with oxaliplatin **or cisplatin** is recommended [II, B].	**100%**
6: Adjuvant treatment	
6a. For patients with stage **≥II** gastric cancer who have undergone surgery without administration of preoperative chemotherapy, adjuvant chemotherapy is recommended [I, A].	100%
6b. For patients who have undergone surgery with clear margins (R0), post-operative RT has no added benefit and should not be given [I, D].	100%
6c. For patients undergoing peri- or post-operative chemotherapy, the addition of post-operative RT has no added benefit and should not be given [I, E].	100%
6d. For patients who have not received preoperative chemotherapy and have not undergone an appropriate D2 lymphadenectomy, adjuvant CRT can be considered [I, C].	100%
6e. For patients who have undergone surgery with involved margins (R1), adjuvant RT or CRT might be considered as an individual recommendation, but is not standard [IV, C].	100%
6f. For patients with MSI-H gastric cancer who have undergone curative surgery, adjuvant ChT **should be carefully considered [**IV**, C].**	**100%**
7: First-line therapy	
7a. First-line chemotherapy with a platinum and fluoropyrimidine is recommended. Oxaliplatin is preferred, especially for older patients [I, A]. S-1 is commonly used in Asian patients [I, A].	100%
7b. Due to higher levels of toxicity and uncertain survival benefit over recommended doublet regimens, first-line taxane-based triplet chemotherapy is not recommended as a standard approach [I, C].	100%
7c. **Fluoropyrimidine monotherapy or in combination with irinotecan or a taxane** can be considered an alternative option for patients who do not tolerate platinum compounds [II, B].	**100%**
7d. If available, the addition of zolbetuximab to ChT can also be considered for patients with claudin-18.2-positive, HER2-negative tumours in the first-line metastatic disease setting.[27,28] (At time of writing, this combination has not been approved by the regulatory authorities).	100%
8: First-line therapy in patients with PD-L1-positive disease	
8a. Nivolumab—chemotherapy is recommended for advanced, untreated gastric, OGJ and oesophageal cancer with a PD-L1 CPS ≥5 [I, A; ESMO-MCBS v1.1 score: 4].	100%
8b. If available, the addition of pembrolizumab to chemotherapy can also be considered for patients with HER2-negative OGJ and gastric tumours in the first-line metastatic disease setting **especially for those with higher levels of tumour PD-L1 expression.**[56]	**100%**
9: First-line therapy in patients with HER2-positive diseases	
9a. Trastuzumab—chemotherapy is recommended in patients with HER2-positive tumours [I, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-A].	100%
10: Surgery for metastatic gastric cancer	
10a. Gastrectomy is not recommended in metastatic gastric cancer unless required for palliation of symptoms [I, D].[61]	100%
10b. Resection of metastases cannot be recommended in general but might be considered as an individual approach in highly selected cases with oligometastatic disease and response to chemotherapy [V, C].	100%
11: Second- and later-line treatment	
11a. Ramucirumab—paclitaxel is recommended for second-line treatment of gastric cancer [I, A; ESMO-MCBS v1.1 score: 2]. Ramucirumab monotherapy is also an option [I, B; ESMO-MCBS v1.1 score: 1].	100%
11b. Where ramucirumab is not available, paclitaxel, docetaxel or irinotecan monotherapy [I, A] or FOLFIRI [II, B] are recommended.	100%
12: Second- and later-line treatment in patients with MSI-H disease	
12a. Pembrolizumab is recommended for second-line treatment of patients with MSI-H/dMMR gastric cancer [II, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-B].	100%

Continued

Table 1. Continued

Recommendations	Acceptability consensus
13: Second- or further-line treatment in patients with HER2-positive disease	
13a. Treatment with trastuzumab is not recommended after first-line therapy in HER2-positive advanced gastric cancer [I, D].	100%
13b. Trastuzumab deruxtecan **(T-DXd)** is recommended **as third- or later-line therapy** for patients with HER2-positive advanced gastric cancer who have received a prior trastuzumab-based regimen [I, A; ESMO-MCBS v1.1 score: 4;]. Re-biopsy **before T-DXd treatment may be considered** when possible**.**	100%
14: Chemotherapy for third- and later-line treatment	
14a. For patients previously treated with two lines of therapy, trifluridine—tipiracil is recommended [I, A; ESMO-MCBS v1.1 score: 3]. Alternative treatments include a taxane or irinotecan [II, B].	100%
15: Supportive care and nutrition	
15a. Care for patients with gastric cancer should include an early palliative care referral and nutritional support [I, A].	100%
15b. **Supportive care including** low-dose olanzapine with dietary support **may** be considered to improve appetite and weight gain [I, B].	**100%**
16: Follow-up, long-term implications and survivorship	
16a. Regular follow-up is recommended for investigation and treatment of symptoms, psychological support and early detection of recurrence [III, B].	100%
16b. Follow-up should be tailored to the individual patient and stage of disease [V, B].	100%
16c. Dietary support is recommended with attention to vitamin and mineral deficiencies [V, B].	100%
16d. In the advanced disease setting, regular follow-up is recommended to detect symptoms of disease progression before significant clinical deterioration [IV, B].	100%
16e. Radiological investigations, specifically CT of the thorax and abdomen, should be carried out every 6-12 weeks in patients who are candidates for further cancer specific therapies [IV, B].	100%

5-FU, 5-fluorouracil; AJCC, American Joint Committee on Cancer; ChT, chemotherapy; CPS, combined positive score; CRT, chemoradiotherapy; CT, computed tomography; CY+, positive peritoneal cytology; dMMR, defective mismatch repair; DOS, docetaxel, oxaliplatin and S-1; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; FDG—PET, [^{18}F]2-fluoro-2-deoxy-D-glucose—positron emission tomography; FOLFIRI, folinic acid, 5-FU and irinotecan; FLOT, fluoropyrimidine, oxaliplatin and docetaxel; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MSI, microsatellite instability; MSI-H, microsatellite instability-high; OGJ, oesophagogastric junction; PD-L1, programmed death-ligand 1; PET, positron emission tomography; R1, microscopic tumour at the margin; RT, radiotherapy; S-1, tegafur—gimeracil—oteracil; T-DXd, trastuzumab deruxtecan; TNM, tumour—node—metastasis; UICC, Union for International Cancer Control; WHO, World Health Organization.

recommendations together with the experts from each of the nine other Asian oncology societies ($n = 20$). All 20 Asian experts provided comments on the pre-meeting survey and one consensus response per society (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226). Only one voting member per Asian society was present at the face-to-face meeting. None of the additional JSMO members and none of the ESMO experts were allowed to vote and were present in an advisory role only (see Methodology in the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2023.102226). All the Asian experts ($n = 20$) approved the revised recommendations.

RESULTS

A. Scientific adaptations of the ESMO recommendations

In the initial pre-meeting survey, the 20 voting Asian experts reported on the 'acceptability' of the 38 recommendations for the diagnosis, treatment and follow-up of patients with GC from the most recent ESMO Clinical Practice Guidelines (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226), in the 16 categories outlined in the text below and in Table 1. A lack of agreement in the pre-meeting survey was established for 23 recommendations (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226), 16 of which were discussed at the face-to-face working meeting in Tokyo to adapt the recently published ESMO Clinical Practice Guidelines[5] and associated ESMO Gastric Cancer Living Guideline v1.1.[17] The remaining seven incidences of discrepancy related to the 'applicability' of the proposed recommendations in certain of the Asian countries/regions and not their 'scientific acceptability' (see Results in the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2023.102226).

1. Epidemiology—recommendations 1a-b

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 1a and b' (Table 1), without change.

In relation to 'recommendation 1b', and as outlined above in the introduction, there is clear evidence that eradication of *H. pylori* is associated with a reduction in the incidence of GC.[15,18-20] As a consequence, population- and endoscopy-based screening programmes have been introduced in high-risk regions such as China, Taiwan, Japan and South Korea, resulting in higher detection rates for early-stage GC and improved mortality.[21-24] Population-based endoscopic screening of asymptomatic individuals is not recommended for countries with a low incidence of GC.[5,17]

2. Diagnosis, pathology and molecular biology—recommendations 2a-c

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 2a-c' (Table 1), without any change to 'recommendation 2b' (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226), following discussion of the use of the

World Health Organization (WHO) criteria for the histological diagnosis of patients in Japan. Currently, it is usual for the histopathological findings for patients in Japan to be reported according to the Japanese Gastric Cancer Association classification,[25] with the WHO classification[26] used only for those entered into global clinical trials. Going forward the intention is to recommend that both classification systems are used together in Japan.

The molecular profiles of each tumour should be determined where possible for metastatic or unresectable GC including human epidermal growth factor receptor 2 (HER2) expression, programmed death-ligand 1 (PD-L1) and microsatellite instability/deficiency in mismatch repair (MSI/dMMR) status validated as predictive biomarkers.[5,17] Knowledge of MSI/dMMR status is important for patients with resectable disease (see 'recommendation 6f' below). Claudin 18.2 [claudin-18 isoform 2 (CLDN18.2)] expression may also be examined using immunohistochemistry (IHC), if the test is available. The therapeutic monoclonal antibody zolbetuximab binds CLDN18.2-positive GC cells and has recently been shown to improve clinical outcomes when combined with chemotherapy (ChT) in the treatment of patients with GC[27,28] (see 'recommendation 7d' Table 1 and Section 8 below).

3. Staging—recommendations 3a-d

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 3a-d' (Table 1), following discussion and revision of 'recommendations 3a and 3c'.

The original 'recommendation 3a' was revised to be more precise, particularly in relation to the inclusion of a computed tomography (CT) scan of the pelvis. Thus, the original ESMO recommendation was reworded as per the additions made in bold text, below and in Table 1.

3a. Initial staging and risk assessment should include physical examination, full and differential blood count, liver and renal function tests, **upper gastrointestinal** endoscopy and a contrast-enhanced CT scan of the thorax **and whole** abdomen **including the** pelvis (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.102226) [V, A, **consensus = 100%**].

In relation to 'recommendation 3c', there was considerable discussion regarding the use of diagnostic laparoscopy. The Japanese experts did not consider routine diagnostic laparoscopy essential for all patients due to the fact that perioperative ChT is not the standard of care for all patients in Japan. Typically, the peritoneal cavity is inspected at the time of surgery with diagnostic laparoscopy part of the procedure before resection. However, the Japanese experts did recommend diagnostic laparoscopy for selected patients with a relatively high risk of peritoneal dissemination such as those with macroscopic type 4 or large type 3 disease as per the Japanese GC treatment guidelines.[25] The Korean experts said that consideration should be given to the feasibility of diagnostic laparoscopy and peritoneal washings in the real-world setting. The proposal was that laparoscopy should only be undertaken if peritoneal seeding was suspected based on CT scans or a physical examination, and positron emission tomography (PET) used if needed to ensure no distant metastases are present, as recommended for the Korean phase III PRODIGY trial.[29] The Chinese experts held the view that diagnostic laparoscopy could improve the diagnostic rates of occult metastasis within the abdominal cavity. Before neoadjuvant therapy (for T3-4 or N+ cases), explorative laparoscopic staging and cytological examination of intraperitoneal washings are recommended in the CSCO guidelines. The representatives of the other oncological societies present thought that the ESMO recommendation would be challenging for some treatment centres.

Thus, the original ESMO recommendation 3c below:

3c. Diagnostic laparoscopy and peritoneal washings for cytology are recommended for patients with resectable gastric cancer who are also candidates for perioperative ChT [III, B]. Patients with CY+ are uncertain candidates for curatively-intended surgical resection, was revised by dividing it into two recommendations (i) for patients with resectable GC recommended for upfront surgery and (ii) those patients with resectable GC recommended for perioperative ChT (see below and Table 1).

3c-i. Diagnostic laparoscopy and peritoneal washings for cytology **should be considered** for **selected** patients with resectable gastric cancer **and a risk of peritoneal metastasis [III, B; consensus = 100%].**

3c-ii. Diagnostic laparoscopy and peritoneal washings for cytology are recommended for patients with resectable gastric cancer who are candidates for perioperative ChT [III, B; **consensus = 100%**].

It should be noted that patients with positive peritoneal cytology (CY+ disease) are uncertain candidates for surgery with curative intent, although some CY+ Asian patients achieve long survival,[30] and the benefits of diagnostic staging laparoscopy and peritoneal washings are uncertain for patients with early cT1-cT2, and cN0 disease.[31-34]

4. Localised gastric cancer—recommendations 4a-d

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 4a, b and d' (Table 1). However, following discussion at the face-to-face meeting, the original 'recommendation 4c' below was deleted **(100% consensus)** and the original 'recommendation 4d' renumbered as 4c in Table 1.

4c. For stage IB-III gastric cancer, peri-operative therapy and radical gastrectomy is recommended [I, A].

This was because in Eastern Asia, upfront D2 gastrectomy followed by adjuvant ChT is still the standard of care for most GC cases due to the fact that GCs are detected at an earlier stage and patients have a more favourable prognosis than most non-Asian GC patient populations.

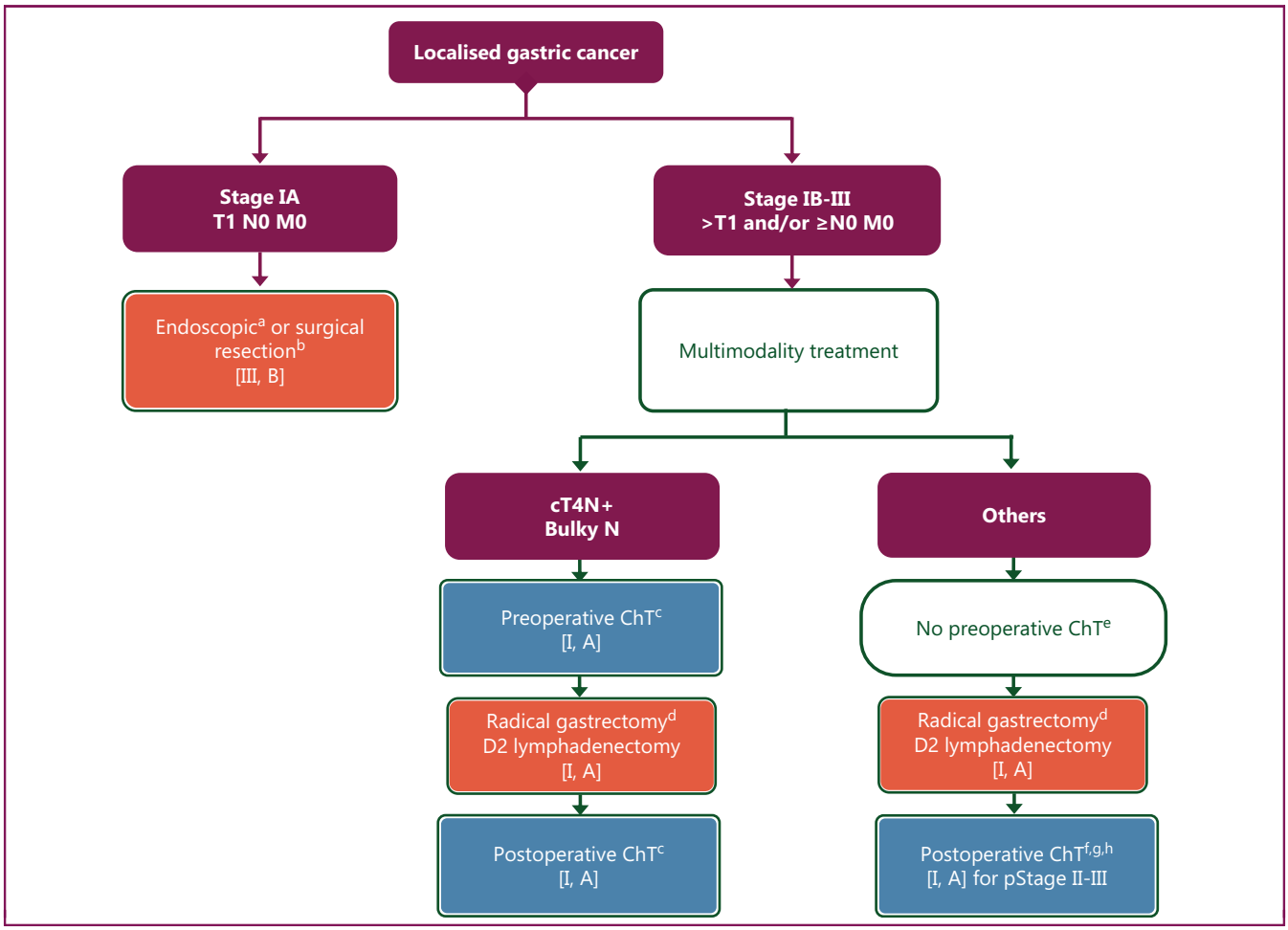

Figure 1. Algorithm for the treatment of localised gastric cancer.
Burgundy boxes: general categories or stratification; orange boxes: surgery; white boxes: other aspects of management; blue boxes: systemic anticancer therapy.
ChT, chemotherapy; MSI-H, microsatellite instability-high; N, node; R1, microscopic tumour at the margin; RT, radiotherapy.
[a]Endoscopic resection indicated if: (i) confined to mucosa; (ii) well-differentiated G1-2; (iii) ≤2 cm; (iv) non-ulcerated. Endoscopic resection to be considered if no more than two expanded criteria are met according to Pimentel-Nunes et al.[79]
[b]Lymph node dissection for T1 tumours may be confined to perigastric lymph nodes and include local N2 nodes (D1+ lymphadenectomy, with variation in nodal groups dissected according to site of tumour).
[c]Peri-operative (pre- and post-operative) chemotherapy should be considered for **selected** patients with stage >IB resectable gastric cancer [I, A]. Doublet/triplet ChT regimens are recommended [II, A].
[d]Subtotal gastrectomy may be carried out if a macroscopic proximal margin of ≥3 cm can be achieved. For cancers of the poorly cohesive/diffuse subtype, a margin of ≥5 cm is advocated.
[e]For patients with stage >II gastric cancer who have undergone surgery without administration of preoperative ChT. A perioperative approach may be considered as adjuvant ChT is less well tolerated than neoadjuvant ChT and neoadjuvant therapy leads to tumour downsizing, allowing for more curative resections.
[f]Doublet ChT containing a fluoropyrimidine plus oxaliplatin or docetaxel for a total duration of 6 months is recommended. S-1 monotherapy for 1 year is also accepted in East Asia as standard adjuvant ChT after D2 gastrectomy. However, S-1 monotherapy has been shown to have limited survival benefits in patients with stage III GC, and doublet regimens are recommended for the adjuvant treatment of these patients.
[g]For patients with an R1 resection, adjuvant RT or ChT might be considered as an individual recommendation but is not standard.
[h]For patients with MSI-H gastric cancers who have undergone surgery, adjuvant ChT should be carefully considered.

A proposed algorithm for the treatment of localised gastric cancer is presented in Figure 1.

5. Perioperative chemotherapy—recommendations 5a-d

The Pan-Asian panel of experts failed to agree with the original ESMO recommendations, 'recommendations 5a-d' (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226).

The original ESMO recommendation, 'recommendation 5a' (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226), proposing perioperative ChT (which is the standard of care in Europe and other Western countries) for patients with stage >IB resectable GC based on two European phase III trials,[35,36] was not accepted by 5 of the 10 Asian oncology societies.

This was because, as stated in Section 4 above, patients in Asia generally present with earlier-stage GC and upfront surgery followed by adjuvant ChT is still the standard of care. The Asian phase III PRODIGY[29] and RESOLVE[37,38] trials of perioperative ChT in patients with cT2-3N+ or cT4Nany and cT4aN+ or cT4bNany patients, respectively, reported a benefit for perioperative ChT with the survival benefit greatest in those patients with cT4N+ disease, as suggested

by the updated analysis of overall survival (OS) from the PRODIGY trial.[39] Of note, the phase III Japanese JCOG 0501 trial failed to show an improvement in OS from the addition of neoadjuvant tegafur—gimeracil—oteracil (S-1) plus cisplatin compared with surgery followed by adjuvant S-1, for patients with type 4 or large type 3 GC.[40] In the Japanese GC treatment guidelines,[41] preoperative ChT is recommended in selected patients with large lymph nodes, and generally in everyday clinical practice in Japan perioperative ChT is only used to treat patients with either bulky lymph node metastases or cT4b disease. Similarly, in Korea and Singapore, perioperative ChT is only considered for the treatment of patients with cT4 or bulky lymph node-positive disease.

Thus, 'recommendation 5a' was revised as per the bold text below and in Table 1, to read as follows:

5a. Peri-operative (pre- and post-operative) ChT **should be considered** for **selected** patients with stage >IB resectable gastric cancer **[I, A; consensus = 100%].**

The original 'recommendation 5b' recommending the use of a triplet ChT regimen, comprising a fluoropyrimidine, a platinum compound and docetaxel perioperatively when possible, was not accepted by 4 of the 10 Asian oncology societies (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226). The data for triplet regimens in Asia are limited.

As a consequence, 'recommendation 5b' was revised to read as follows below and in Table 1:

5b. Doublet/triplet ChT regimens are recommended [II, A; consensus = 100%].

A triplet ChT regimen comprising a fluoropyrimidine, oxaliplatin and docetaxel (FLOT) has been shown to demonstrate high efficacy in fit patients with GC in a phase II-III European trial.[42] For patients unable to tolerate a triplet regimen, a combination of a fluoropyrimidine and oxaliplatin may be an alternative.

The original 'recommendation 5c' recommending the triplet FLOT regimen (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226) was not accepted by four of the Asian oncology societies.

The experts from both China and Japan support the use of doublet ChT regimens, and whether triplet FLOT ChT is suitable for use in Asian patients in this setting remains to be established. However, data from the Korean phase III PRODIGY trial suggest that the addition of preoperative docetaxel, oxaliplatin and S-1 (DOS) to D2 gastrectomy and adjuvant S-1 leads to significant tumour downstaging and improved progression-free survival (PFS) and OS, with an acceptable safety profile, in patients with locally advanced gastric or OGJ adenocarcinomas and should be considered as a treatment option for resectable advanced GC.[29,39] Of note, the recently reported results of the phase III MATTERHORN study comparing FLOT plus durvalumab versus FLOT plus placebo, which included around 20% of patients from Asian countries, raised no major safety concerns resulting from the addition of durvalumab.[43]

As a consequence, the original 'recommendation 5c' was reworded to read as follows, below and in Table 1.

5c. For patients who are candidates for a triplet ChT regimen, FLOT [ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: A] or DOS [ESMO-MCBS v1.1 score: A] are recommended [II, A; consensus = 100%].

The original 'recommendation 5d' (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226) was also not accepted by four of the Asian oncology societies and as a consequence was reworded as per the bold text below and in Table 1 to read as follows:

5d. For patients **who are candidates** for **doublet perioperative** ChT, a combination of a fluoropyrimidine with oxaliplatin **or cisplatin** is recommended [II, B; **consensus = 100%].**

It should be noted that many of the Asian experts did not favour the use of perioperative ChT at this time, and even for stage III disease adjuvant doublet ChT is generally the preferred treatment strategy. The results of trials that have recruited patients with earlier-stage gastric and OGJ cancers than the Korean PRODIGY trial[29] and the Chinese RESOLVE[37] trial of perioperative S-1 plus oxaliplatin (SOX), which showed a clinically meaningful improvement compared with adjuvant therapy, are eagerly awaited.

6. Adjuvant treatment—recommendations 6a-f

The Pan-Asian panel of experts failed to agree with the original ESMO recommendations, 'recommendations 6a and 6f' (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226). The comments relating to 'recommendations 6b, d and e' were unrelated to their acceptability from a scientific point of view, and 'recommendations 6b-e' were accepted at the face-to-face meeting without change (100% consensus).

There was considerable discussion around the original ESMO recommendation, 'recommendation 6a' (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226), with regard to the statement that patients with resected stage ≥IB GC should receive adjuvant ChT. As a consequence, it was agreed that adjuvant ChT should be recommended only for those patients with stage ≥II GC based on data from the randomised phase III ACTS-GC trial of S-1, the phase III CLASSIC trial of capecitabine-oxaliplatin (CAPOX) and the phase III JACCRO GC-07 trial of S-1 plus docetaxel.[44-47]

Both S-1 for 1 year and CAPOX for 6 months are currently accepted in East Asia as standard adjuvant ChT regimens for the treatment of stage II or III GC, after D2 gastrectomy.[48,49] S-1 monotherapy, however, has been shown to have limited survival benefits in patients with stage III GC, and the

doublet regimens CAPOX, SOX or S-1 plus docetaxel are recommended for the adjuvant treatment of these patients.[47,48,50] The optimal number of cycles of CAPOX or SOX adjuvant ChT for patients with stage III GC after D2 resection is being investigated.[51]

Thus, the wording of 'recommendation 6a' was revised as per the bold text below and in Table 1 to read as follows.

6a. For patients with stage **≥II** gastric cancer who have undergone surgery without administration of preoperative ChT, adjuvant ChT is recommended [I, A; **consensus = 100%**].

In the case of the original ESMO recommendation, 'recommendation 6f' (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226), regarding patients with MSI-high (MSI-H) GC who have undergone potentially curative surgery, the representatives of 6 of the 10 Asian oncology societies did not accept the part of the recommendation relating to adjuvant therapy. The general opinion was that there were insufficient data and that the role of adjuvant ChT in patients with dMMR/MSI-H GC was not clear,[5] although some Asian clinicians still consider adjuvant ChT for this group of patients. There was some agreement regarding the role of ChT if downstaging of the tumour was required before surgery.

Thus, 'recommendation 6f' was revised to read as follows and in Table 1, with 100% consensus.

6f. For patients with MSI-H gastric cancer who have undergone curative surgery, adjuvant ChT **should be carefully considered [**IV**, C; consensus = 100%].**

7. First-line therapy—recommendations 7a-d

An algorithm for the proposed first-line treatment of Asian patients with unresectable advanced and metastatic GC is presented in Figure 2.

'Recommendations 7a, b and d' were accepted at the face-to-face meeting without change (100% consensus). The Pan-Asian panel of experts failed to agree with the original ESMO recommendation 'recommendation 7c' (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226). In Japan, docetaxel plus S-1, S-1 monotherapy, 5-fluorouracil (5-FU) plus paclitaxel and 5 FU/l-leucovorin (LV) are all used in the first-line setting for patients for whom fluoropyrimidine plus platinum therapy is not feasible.[41] Thus, recommendation 7c was revised as per the bold text below and in Table 1 to read as follows:

7c. Fluoropyrimidine monotherapy or in combination with irinotecan or a taxane can be considered an alternative option for patients who do not tolerate platinum compounds **[**II, B; **consensus = 100%].**

It should be noted that recent results from the French phase III GASTFOX-PRODIGE 51 study have reported a significantly superior OS with modified FLOT when compared with FOLFOX,[52] suggesting that a triplet regimen may be an option in this setting. In contrast, the Japanese JCOG1013 failed to demonstrate an improvement in OS for S-1 plus cisplatin plus docetaxel when compared with S-1 plus cisplatin.[53] However, when the low rate of use of subsequent ChT in the GASTFOX study, compared with Asian trials, is taken into account, the results are currently not applicable to the treatment of Asian patients.

In relation to 'recommendation 7d', the global phase III SPOTLIGHT trial has recently shown the monoclonal antibody zolbetuximab, which targets the transmembrane protein CLDN18.2, to have efficacy in patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or OGJ adenocarcinomas, when combined with FOLFOX6.[27] Zolbetuximab treatment showed a significant reduction in the risk of disease progression or death compared with placebo [hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.60-0.94, $P = 0.0066$]. In the phase III GLOW trial, zolbetuximab was combined with CAPOX in patients with HER2-negative, locally advanced unresectable or metastatic gastric and OGJ cancers, and met its primary endpoint of PFS (HR 0.687, 95% CI 0.544-0.866, $P = 0.0007$) and key secondary endpoint of OS (median 14.39 months versus 12.16 months, HR 0.771, 95% CI 0.615-0.965, $P = 0.0118$), with the benefits greater in Asian than in non-Asian patients.[28] As a consequence, the zolbetuximab licence application has been granted priority review by the Food and Drug Administration (FDA), based on data from both the SPOTLIGHT and GLOW trials.[27,28] Zolbetuximab in combination with an oxaliplatin-based ChT regimen may represent a new first-line treatment option in these patients (see 'recommendation 7d', Table 1).

At this stage, it is difficult to select either ChT plus zolbetuximab or ChT plus programmed cell death protein 1 (PD-1) inhibitor because of the absence of direct comparisons. Nevertheless, zolbetuximab might be the preferred choice for patients with PD-L1-negative or low expression [i.e. combined positive score (CPS) <5] and CLDN18.2-positive tumours. When dealing with patients who have overlapping characteristics, such as CPS ≥5 and CLDN18.2 positivity, choosing between these two regimens becomes less clear-cut, and either approach could be a reasonable treatment option.

8. First-line therapy in patients with PD-L1-positive disease—recommendations 8a-c

The Pan-Asian panel of experts accepted completely (100% consensus) the original ESMO recommendation, 'recommendation 8a' for the addition of the PD-1 inhibitor nivolumab to ChT in the treatment of patients with advanced, untreated gastric, OGJ and oesophageal cancer with a PD-L1 CPS ≥5 (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226) based on data from the phase III CheckMate 649 study.[54]

However, in relation to the original 'recommendation 8b' (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226), which was actually a

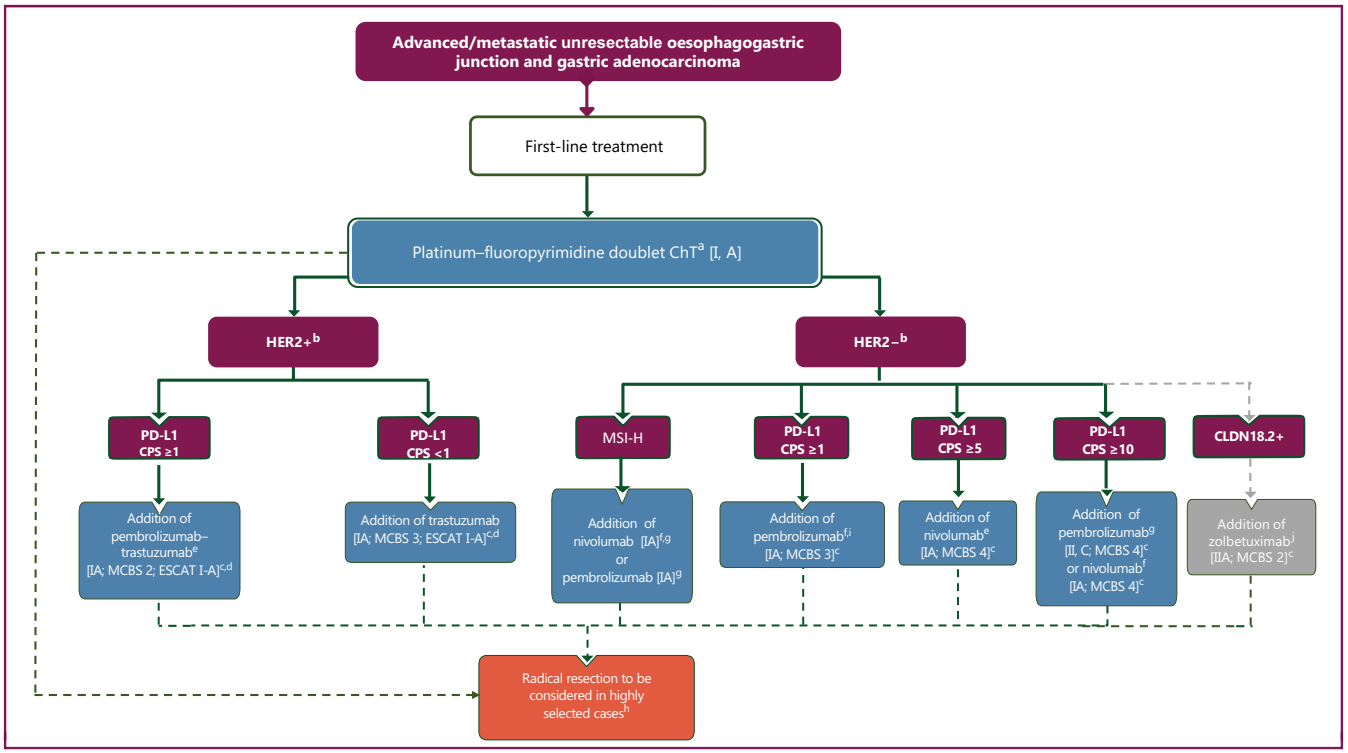

Figure 2. Algorithm for the first-line treatment of unresectable advanced or metastatic oesophagogastric junction and gastric cancers.
Burgundy boxes: general categories or stratification; orange boxes: surgery; white boxes: other aspects of management; blue boxes: systemic anticancer therapy; and grey boxes for agents that are not yet approved.
5-FU, 5-fluorouracil; CHMP, Committee for Medicinal Products for Human Use; ChT, chemotherapy; CPS, combined positive score; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; FISH, fluorescence *in situ* hybridisation; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; MCBS, ESMO-Magnitude of Clinical Benefit Scale; OGJ, oesophagogastric junction; PD-L1, programmed death-ligand 1; S-1, tegafur—gimeracil—oteracil.
[a]Recommended platinum compounds are oxaliplatin or cisplatin. Oxaliplatin is preferred, especially for older patients. Recommended fluoropyrimidines are intravenous 5-FU, oral capecitabine or oral S-1. Fluoropyrimidine monotherapy or a fluoropyrimidine in combination with irinotecan or a taxane can be considered as an alternative option for patients who do not tolerate platinum compounds.
[b]HER2 IHC 3+ or IHC 2+ and FISH ≥2.
[c]ESMO-MCBS v1.1[80] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[d]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[81]
[e]Nivolumab—ChT is recommended for advanced, untreated gastric and OGJ cancer with a PD-L1 CPS score ≥5 (FDA approved without PD-L1 CPS restriction, EMA approved for PD-L1 CPS ≥5). Higher PD-L1 expression levels are associated with higher efficacy. CPS 1-4 is associated with borderline efficacy (e.g. HR 0.95 in CheckMate-649[82]).
[f]Pembrolizumab—ChT is recommended for advanced, untreated gastric, OGJ and oesophageal adenocarcinoma with a PD-L1 CPS score ≥1 (FDA approved without PD-L1 CPS restriction, EMA-CHMP recommended for gastric and OGJ cancer with a PD-L1 CPS ≥1 [for oesophageal adenocarcinoma with a CPS ≥10]). Higher PD-L1 expression levels are associated with higher efficacy. CPS 1-9 is associated with borderline efficacy. Based on positive phase III study outcomes, some other PD-1 ICIs are available in China, e.g. tislelizumab, sintilimab, sugemalimab, toripalimab.
[g]Subgroup analyses from first-line randomised trials such as CheckMate-649, KEYNOTE-062 and KEYNOTE-859, amongst others, consistently demonstrate a large benefit if PD-1 ICIs are used first line for dMMR/MSI-high gastric cancer, including OGJ adenocarcinomas. This was also demonstrated in pooled data analyses from different immunotherapy studies.[57,83] Whether chemotherapy should be combined with PD-1 ICIs or if PD-1 ICIs should be given alone is an open question. If a fast response is needed due to high symptom burden, involvement of vital organs, etc., an initial phase of combination therapy should be considered. PFS but not OS data tended to be better with chemotherapy combination therapy compared with PD-1 ICI.[57]
[h]Gastrectomy is not recommended for metastatic gastric cancer unless required for palliation of symptoms. Resection of metastases cannot be recommended in general but might be considered as an individual approach in highly selected cases with oligometastatic disease and response to ChT.
[i]ESCAT I-A.
[j]Not approved.

statement of approval, it was considered to be based on data from a trial that was too oesophageal cancer focussed,[55] and the recommendation was that it should be removed (**100% consensus**).

In relation to 'recommendation 8c' (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226), four of the Asian oncology societies did not accept the use of the addition of the PD-1 inhibitor pembrolizumab to ChT, and currently it is not approved by either the European Medicines Agency (EMA) or FDA in this clinical setting. However, an interim analysis of the phase III KEYNOTE-859 trial has established a clinical benefit from the addition of pembrolizumab to platinum-based ChT for patients with locally advanced or metastatic HER2-negative gastric or OGJ cancer.[56] The benefit was seen in the intention-to-treat (ITT) population (all comers) but was more marked in those patients with higher tumour PD-L1 expression.[56] For the ITT population, the median OS was

12.9 months for patients receiving the pembrolizumab—ChT regimen versus 11.5 months for those receiving ChT alone (HR 0.78, 95% CI 0.70-0.87, $P < 0.0001$).[56] In patients with a PD-L1 CPS of $\geq$1 it was 13.0 months versus 11.4 months (HR 0.74, 95% CI 0.65-0.84, $P < 0.0001$) and in patients with a PD-L1 CPS of $\geq$10 it was 15.7 months versus 11.8 months (HR 0.65, 95% CI 0.53-0.79, $P < 0.0001$).[56] Significantly, patients with MSI-H GC have already demonstrated high response rates and excellent long-term outcomes when treated with anti-PD-1 monotherapy,[57,58] and it has been proposed that MSI-H status may be a biomarker for pembrolizumab therapy among patients with advanced gastric/OGJ cancer irrespective of the line of therapy in which it is used (see Section 12 below). However, it remains unclear whether anti-PD-1 therapy alone or in combination with ChT is the preferred treatment for MSI-H patients. Of note, the benefit of anti-PD-1 therapy for MSI-H patients is observed regardless of CPS status.

Since there is no direct comparison of anti-PD-1—ChT versus zolbetuximab—ChT for patients with claudin 18.2-positive disease and a high CPS (CPS 5 or 10), either treatment would be a treatment option for biomarker overlapping patients.

'Recommendation 8c' was therefore modified as per the bold text below and Table 1, and renumbered as 8b, to read as follows:

8b. If available, the addition of pembrolizumab to ChT can also be considered for patients with HER2-negative OGJ and gastric tumours in the first-line metastatic disease setting **especially for those with higher levels of tumour PD-L1 expression [II, A; consensus = 100%].**

Going forward it was proposed that an appropriate PD-L1 CPS cut-off should be determined and the level of recommendation for pembrolizumab use should be refined to take into account the PD-L1 CPS levels.

9. First-line therapy in patients with HER2-positive disease—recommendation 9a

The Pan-Asian panel of experts accepted completely (100% consensus) the original ESMO recommendation, 'recommendation 9a', without change (Table 1) based on the results of the phase III ToGA trial.[59]

However, it should be noted that the addition of pembrolizumab to trastuzumab—ChT in the KEYNOTE-811 trial, in patients with previously untreated unresectable or metastatic HER2-positive gastric or OGJ adenocarcinomas, has been shown to significantly improve PFS (median 10.0 versus 8.1 months, HR 0.72, 95% CI 0.60-0.87, $P = 0.0002$) in all patients at a median follow-up of 28.4 months. In patients with a PD-L1 CPS $\geq$1, the median PFS was 10.9 versus 7.3 months (HR 0.71, 95% CI 0.59-0.86).[60] However, the median OS data for the addition of pembrolizumab to trastuzumab—ChT failed to meet the criteria for superiority over trastuzumab—ChT plus placebo.[60] The objective response rates also favoured those patients receiving pembrolizumab [72.6% (95% CI 67.6% to 77.2%) versus 59.8% (95% CI 54.4% to 65.0%)] when compared with trastuzumab—ChT plus placebo. The addition of pembrolizumab to trastuzumab—ChT has been approved by the FDA. The final OS outcomes from this trial[60] are required to establish the long-term clinical benefits of this combination. Thus, as the EMA approval is limited to patients with CPS $\geq$1 supported by an exploratory subgroup analysis, it is not eligible for ESMO-MCBS scoring. However, if available, trastuzumab—ChT plus pembrolizumab can be considered for patients with HER2-positive gastric cancer and a CPS $\geq$1 (see Figure 2).

10. Surgery for metastatic gastric cancer—recommendations 10a-b

The Pan-Asian panel of experts accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 10a and b', without change (Table 1), based on the results of the phase III REGATTA trial (in patients from Japan, South Korea and Singapore with advanced gastric cancer and a single non-curable factor), which showed that gastrectomy followed by ChT (S-1 plus cisplatin) did not show any survival advantage over ChT alone.[61]

Resection or ablation of metastases may be considered on an individual basis for patients with oligometastatic disease and a response to ChT, based on expert opinion, but the data to support this are limited.[62,63]

The addition of hyperthermic intraperitoneal chemotherapy following surgery has also been explored[64-66] but confirmation from larger trials is required.

Radiotherapy can be considered for patients with metastatic disease for symptom control or improving quality of life, but was not discussed at the face-to-face meeting.

11. Second- and later-line treatment—recommendations 11a-b

The Pan-Asian panel of experts accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 11a and b', without change (Table 1) based on well-established trial data.[67,68]

An algorithm for the proposed second-line treatment of Asian patients with unresectable advanced and metastatic GC is presented in Figure 3.

12. Second- and later-line treatment in patients with MSI-H disease—recommendation 12a

The Pan-Asian panel of experts accepted completely (100% consensus) the original ESMO recommendation, 'recommendation 12a', without change (Table 1) based on the results of the phase II KEYNOTE-158 trial of pembrolizumab monotherapy in patients with previously treated advanced MSI-H GC.[69]

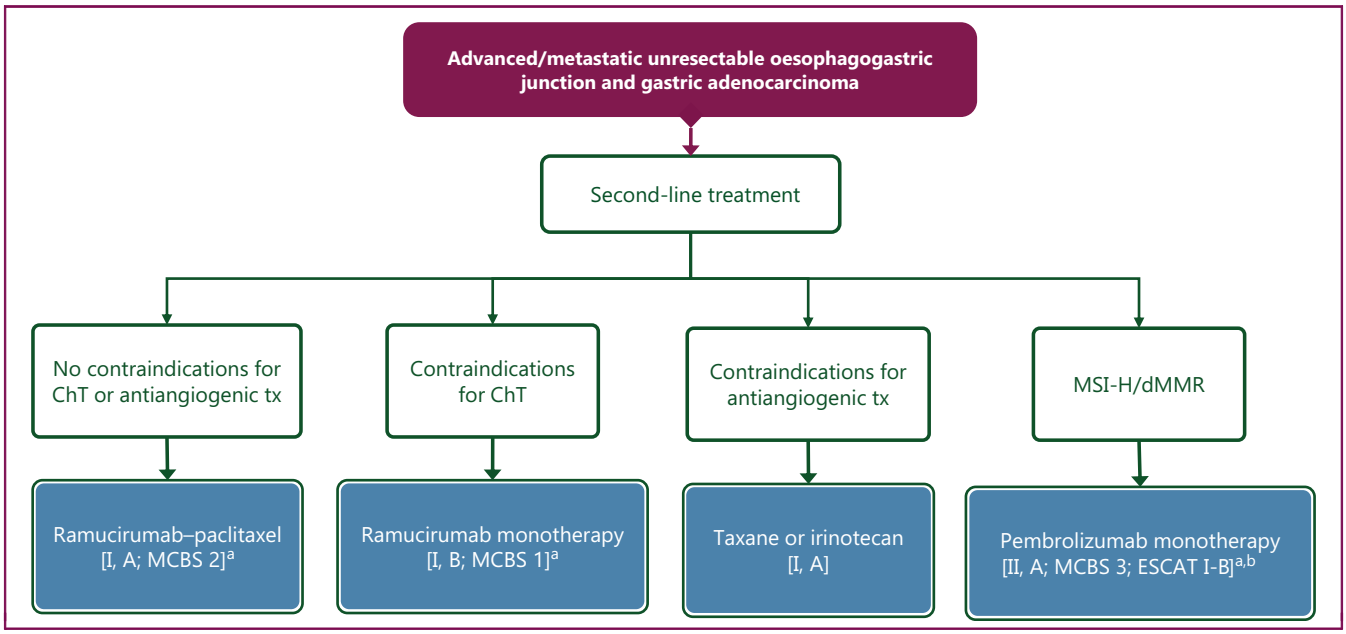

Figure 3. Algorithm for the second-line treatment of unresectable advanced or metastatic oesophagogastric junction and gastric cancers.
Burgundy boxes: general categories or stratification; white boxes: other aspects of management; blue boxes: systemic anticancer therapy.
ChT, chemotherapy; dMMR, mismatch repair deficient; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MSI-H, microsatellite instability-high; tx, treatment.
[a]ESMO-MCBS v1.1[80] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[b]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[81]

13. Second or further lines of treatment in patients with HER2-positive disease—recommendations 13a-b

The Pan-Asian panel of experts accepted completely (100% consensus) the original ESMO recommendation, 'recommendation 13a', without change (Table 1).

However, the Asian experts did not accept that there was evidence in Asian patients to support the use of trastuzumab-deruxtecan (T-DXd) in the second-line setting ('recommendation 13b'). T-DXd is approved only for use as third- or later-line therapy in Asia based on the results of the phase II DESTINY-Gastric01 trial in which T-DXd was compared with ChT in HER2-positive Asian GC patients who had received at least two previous regimens, including a fluoropyrimidine, a platinum agent and trastuzumab, and which reported a survival benefit for the T-DXd-treated patients.[70] Comparable data have been reported for a single-arm study in non-Asian GC patients.[71] The single-arm, phase II, DESTINY-Gastric02 trial demonstrated the efficacy of T-DXd in Western patients after first-line therapy, with a median OS of 12.1 months (95% CI 9.4-15.4 months), median duration of response of 8.1 months (95% CI 5.9 months-not estimable) and median PFS of 5.6 months (95% CI 4.2-8.3 months).[72]

The original 'recommendation 13b' was therefore reworded as per the bold text below and in Table 1, to read as follows:

13b. Trastuzumab deruxtecan **(T-DXd)** is recommended **as third- or later-line therapy** for patients with HER2-positive advanced gastric cancer who have received a prior trastuzumab-based regimen [I, A; ESMO-MCBS v1.1 score: 4; **consensus = 100%].** Re-biopsy **before T-DXd treatment may be considered** when possible**.**

14. Chemotherapy for third- and later-line treatment—recommendation 14a

The Pan-Asian panel of experts accepted completely (100% consensus) the original ESMO recommendation, 'recommendation 14a', without change (Table 1).

Trifluridine—tipiracil[73] or irinotecan or taxane therapy (if not used until third line)[67] could be a treatment option. Nivolumab is also an option if not already used first line, based on the results of the ATTRACTION-2 trial.[74] Nivolumab is currently approved in Japan, South Korea, Singapore and Taiwan, for use as third- or later-line therapy in heavily pretreated patients with unresectable advanced or recurrent GC/OGJ cancer. However, the prioritisation of these regimens is difficult to decide in the absence of a comparison in randomised controlled trials. Apatinib is an option in China based on the results of a randomised phase III trial.[75] However, after the global ANGEL trial failed to show a survival advantage,[76] apatinib is not available for use in any other country.

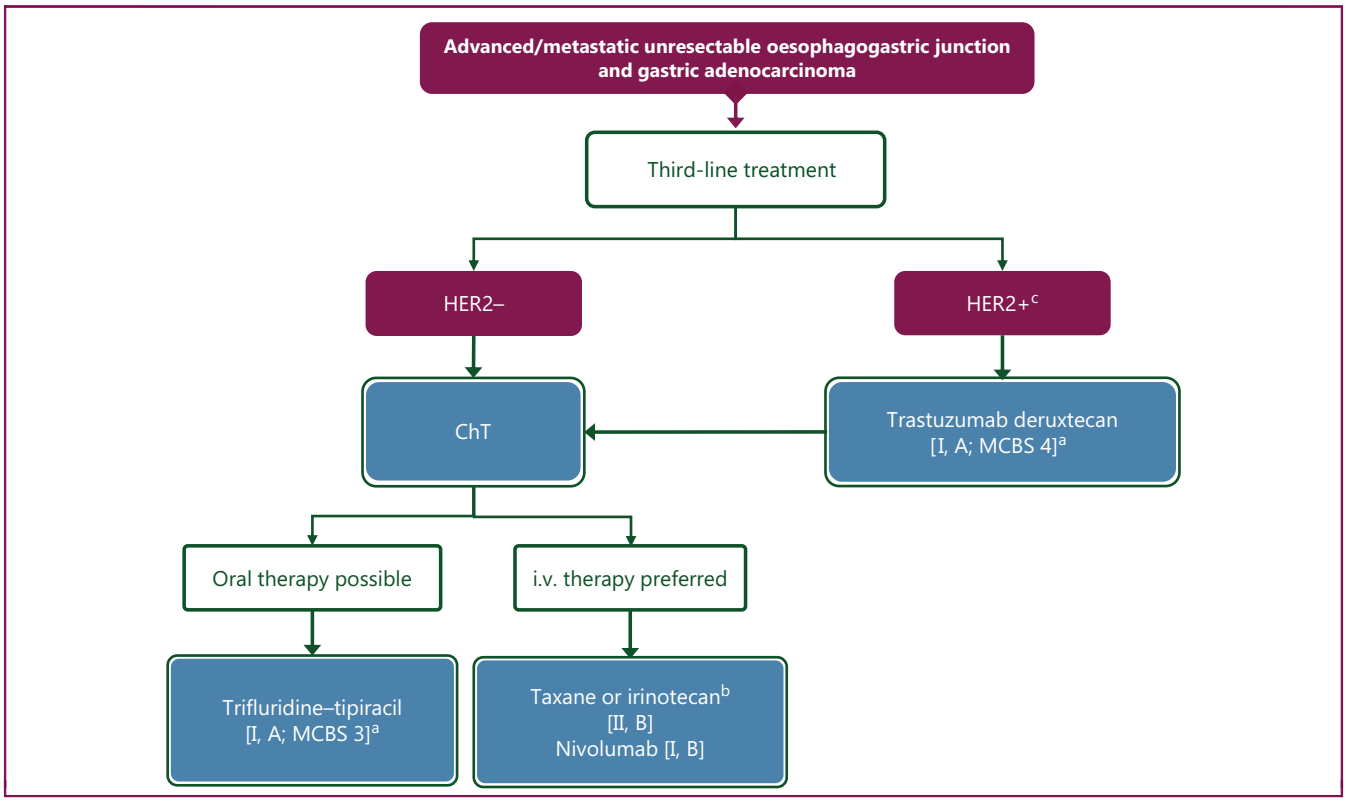

Figure 4. Algorithm for the third-line treatment of unresectable advanced or metastatic oesophagogastric junction and gastric cancers.
Burgundy boxes: general categories or stratification; white boxes: other aspects of management; blue boxes: systemic anticancer therapy.
ChT, chemotherapy; i.v., intravenous; MCBS, ESMO-Magnitude of Clinical Benefit Scale.
[a]ESMO-MCBS v1.1 (112) was used to calculate scores for therapies/indications approved by the European Medicines Agency or Food and Drug Administration. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[b]If not given previously for advanced/metastatic disease.
[c]HER2 IHC 3+ or IHC 2+ and FISH ≥2.

An algorithm for the proposed third-line treatment of Asian patients with unresectable advanced and metastatic GC is presented in Figure 4.

15. Supportive care and nutrition—recommendations 15a-b

The Pan-Asian panel of experts accepted completely (100% consensus) the original ESMO recommendation, 'recommendation 15a' (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226), without change (Table 1), with a recent randomised phase III trial demonstrating a 3-month survival benefit for patients who received ChT.[77]

However, the Asian experts thought that the original 'recommendation 15b' was too strong based on one trial[78] and the recommendation was revised as per the bold text below and in Table 1, to read as follows:

15b. Supportive care including low-dose olanzapine with dietary support **may** be considered to improve appetite and weight gain [I, B**; consensus = 100%].**

16. Follow-up, long-term implications and survivorship —recommendations 16a-e

The Pan-Asian panel of experts accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 16a-e' (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226), without change (Table 1).

Follow-up should be tailored to the needs of the individual patient with dietary support as outlined in the ESMO guidelines.[5,17]

B. Applicability of the recommendations

Following the face-to-face meeting in Tokyo, the Pan-Asian panel of experts agreed and accepted completely (100% consensus) the revised ESMO recommendations for the treatment of GC in patients of Asian ethnicity (Table 1). However, the applicability of each of the guideline recommendations is impacted by the individual drug and testing approvals and reimbursement policies for each Asian country. The drug and treatment availability for the regions represented by each of the 10 participating Asian

oncological societies is summarised in Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2023.102226, and individually for each region in Supplementary Tables S5-S14, available at https://doi.org/10.1016/j.esmoop.2023.102226.

There are striking differences between the regions represented in terms of their approval of the newer agents and in their treatment and testing reimbursement policies. For example, Japanese GC patients (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2023.102226) have access to all the recommended cancer therapies and testing services and all patients receive public assistance so that their out-of-pocket medical expenses are no more than 30% of the total costs (see paragraph on Japan below). Indonesia (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2023.102226), Korea (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2023.102226) and Malaysia (Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2023.102226) have access to nearly all the recommended cancer therapies and testing services but without the generous reimbursement policy of Japan. Similarly, Singapore has approval for nearly all the diagnostic tests and new drugs (Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.2023.102226) but everyone is required to pay for their treatment, using a complicated system whereby patients can pay out of their national savings scheme or private health insurance, with a means-tested 'safety net' for those who cannot afford to pay. In India, although there are fewer approvals and for the most part only IHC testing is reimbursed (Supplementary Table S10, available at https://doi.org/10.1016/j.esmoop.2023.102226), most of the ChT agents and some of the newer agents are available in government hospitals with cancer services and are accessible to most patients at modest or no cost (see paragraph on India below). However, ~65% of patients pay personally, in full, for the newer treatments and tests. In the Philippines, treatment is concentrated in urban centres such as Manila, and although most treatments and tests are available (Supplementary Table S11, available at https://doi.org/10.1016/j.esmoop.2023.102226), none are reimbursed. Also, treatments and tests can be approved by the Philippine FDA (PFDA) but not be approved by the Philippine National Drug Formulary and therefore cannot be accessed by government centres. The patterns of approvals are similar for Taiwan and Thailand (Supplementary Tables S12 and S13, available at https://doi.org/10.1016/j.esmoop.2023.102226) with limited reimbursement for testing and generally no reimbursement for the newer treatments. In China (Supplementary Table S14, available at https://doi.org/10.1016/j.esmoop.2023.102226) most of the tests are approved and patients only have to meet 20% of the approved testing costs. There would appear to be more limited approvals for the newer therapies in China with only trastuzumab for the treatment of HER2-positive advanced GC in the first-line setting being subsidised (patient out-of-pocket cost capped at 30%). China also has agents that are manufactured and uniquely approved for use in China (Supplementary Table S14, available at https://doi.org/10.1016/j.esmoop.2023.102226).

The health care systems of the more uniformly affluent countries such as Japan, Korea and Singapore offer a higher proportion of their populations access to all levels of cancer care not only due to these countries having the highest rates of drug approvals and/or better public reimbursement policies, but also due to a higher percentage of their populations being able to purchase or obtain cancer care through their employment or private medical cover. In mainland China, India and the Philippines, the treatment is more polarised, with patients in the poorer rural and more remote communities having limited access to specialist treatment centres, with the best cancer care being associated with the centres of urbanisation within these countries. The individual statements, from the experts representing each Asian oncological society, describing the availability and access to optimal diagnostic and molecular testing and the latest drug therapies for the individual regions they represent are presented in the paragraphs below.

CSCO

Mainland China (China) has a universal medical insurance system, which aims to cover all residents and provide them with basic medical security and operates in conjunction with private health care providers. Public health care is delivered through a tiered system, including national hospitals, regional hospitals and community health centres. In China, over 90% of GC patients will qualify for varying degrees of reimbursement through the universal medical insurance system, but reimbursement does not cover all of a patient's medical expenses. The drugs available for the treatment of GC include the following ChT drugs: 5-FU, capecitabine, S-1, cisplatin, oxaliplatin and the taxanes docetaxel and paclitaxel, and 80% of the costs for all of the diagnostic tests except next-generation sequencing (NGS) are covered by the national medical insurance system. However, of the newer drugs, only trastuzumab for the treatment of HER2-positive GC is subsidised (70% of the cost), and disitamab vedotin and apatinib which are uniquely approved in China for use in the third-line setting for the treatment of patients with recurrent or metastatic GC. T-DXd is not approved for use in either second- or third-line settings. The reimbursement of targeted drugs depends on whether they are included under the universal medical insurance in China. If a drug is not included under the universal medical insurance scheme, patients may need to pay 100% of its cost. Typically, only 10% of patients pay in full (out of pocket) for treatment, with maybe 30% of patients having additional private insurance, and the remainder covered under the universal medical insurance scheme and then reimbursed by their private insurance.

The average approval time for new drugs is around 6-12 months. However, after a new drug is approved, additional steps are involved before it becomes readily available for use by the clinicians and patients. The time it takes for a

drug to become available after approval varies, depending on the complexity of the manufacturing process and other logistical considerations, with imported drugs taking longer due to transportation and customs inspection. The biggest limiting factors to accessing new treatments and diagnostics are pricing and policy. Reimbursement and pricing policies can impact access to new treatments and diagnostics, with cost sometimes being a significant barrier to access. Finally, the availability and accessibility of new treatments can vary across different health care facilities and regions in China. In rural areas, under-resourced health care settings can restrict patient access to certain treatments.

ISHMO

In Indonesia, the universal health care system (UHC) covers most of the health services. However, although almost 80% of Indonesians are covered by the UHC, there are individuals who also have their own private medical insurance or whose health care is covered by their employer. The use of 5-FU-based ChT (including oxaliplatin or irinotecan regimens) as first-line or second-line therapy is reimbursed. Biomarker testing is available but not all tests are reimbursed. New technology-based tests (e.g. NGS) are not reimbursed. In Indonesia, new drugs/agents firstly have to receive approval from the Indonesian Food and Drug Authority (Indonesian FDA). Then after 2 years an application can be made for the drug to be included in the national formulary which is a list of medications that are eligible to be given to patients under the UHC scheme. However, due to the high burden of health care costs, especially for cancer treatment, it can sometimes take years, multiple scientific evaluations and cost-effectiveness analyses/health technology assessment, for a new drug to be listed under the national formulary for UHC. Thus, most of the drugs are not available or reimbursed for patients with GC. Drugs are approved for very specific indications and currently nivolumab and zolbetuximab are excluded for the treatment of GC. The biggest limiting factor for the treatment of GC patients in Indonesia is access to treatment.

ISMPO

Most of the ChT drugs and many of the newer drugs for the treatment of GC are available to patients in India (Supplementary Table S10, available at https://doi.org/10.1016/j.esmoop.2023.102226). However, there is a public health care system with a scheme based on patient income that covers ∼35% of patients with the remaining 65% of patients treated privately. Typically, patients in the private sector pay 100% of their treatment costs, 65% of patients paying in full (out of pocket) for their treatment, and the remaining 20% and 15% of patients paying via private or employers' insurance, respectively. Patients treated in the public sector typically pay 20%-30% of their treatment costs out of their own pockets. Approximately 75% of patients pay for their own newer diagnostic tests. New drugs are typically approved 1-2 years after approval in the United States and become available to clinicians ∼6 months after approval. The biggest limiting factor to accessing new treatments for patients with GC is cost. Similarly, the biggest limiting factor for accessing new biomarker-related diagnostic tests is cost, as most patients are paying 100% of the cost themselves.

JSMO

In Japan, the government strictly regulates medical costs to keep them affordable. Depending on the family's income and the age of the insured, patients are responsible for paying 10%, 20% or 30% of their medical costs, with the government paying the remainder. All GC patients are eligible for government public assistance. Thus, a patient's out-of-pocket medical expenses are never >30% of the total. Older patients (≥70 years) who are covered by SHSS (senior health insurance) only pay 10% out of their own pockets, whilst, for patients <70 years of age, who have applied for a high-cost medical expense benefit beforehand, the monthly patient payment will be no more than a pre-fixed ceiling amount (depending on their income). There is no employers'/social insurance. For new drugs approved by the EMA or FDA it takes ∼6 months from the time of application to approval and ∼3 months after that before they become available to the clinicians if a first indication, and less if a second indication. The biggest limiting factor is that new drugs may not be approved in Japan if Japanese patients are not included in the clinical trials of these drugs, and if a new diagnostic test is not approved, the patient has to pay in full.

KSMO

In Korea, cover of health care costs is provided to all Korean citizens, including foreigners who have lived in Korea for >6 months, by the National Health Insurance (NHI) system. Cancer patients are categorised as having 'serious disease' and only pay 5% of the total cost including diagnostics, drugs and treatment, which are decided by the Health Insurance Review and Assessment (HIRA) committee. However, with the emergence of many expensive drugs, the limited source of the NHI budget is becoming a big issue. Most of the cytotoxic chemotherapeutic agents are reimbursed. Among the targeted/immunotherapy drugs recommended in the guideline, trastuzumab and nivolumab are reimbursed in the first-line setting, and ramucirumab in the second-line setting. However, T-DXd and nivolumab are not reimbursed for use in later lines (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2023.102226). Thus, the approval of a drug does not always translate into reimbursement. In addition to the NHI coverage, patients with private insurance can pay a part of their health care costs including those for non-reimbursed, expensive new drugs, based on their individual private insurance policy. Conversely, agents with high-level evidence can be reimbursed in the absence of approval which usually takes 1.5-2 years. Typically, only 10% of patients in Korea pay in full (out of pocket) for their treatment, with 15% covered by private insurance and the remaining 75% of patients covered by NHI. The biggest limiting factor to

accessing new treatments is reimbursement, and the requirement for more self-payment. This is because Korea has been categorised as a developed country resulting in the costs of drugs being set at a much higher level than they were previously. In relation to the diagnostic tests, there are no big concerns when compared with drug availability, but recently there have been concerns raised when the companion diagnostics associated with the newer drugs require specific machines which are not available in the pathology laboratories of all the hospitals. In addition, there are concerns about the quality of some of the diagnostic testing and there is a requirement for training to achieve standardisation across the different treatment centres and laboratories. These are all issues that need to be addressed.

MOS

In Malaysia the basic cancer treatments are heavily subsidised by the government and there is no national insurance policy. For example, 90% of the cost of essential ChT agents for the treatment of GC, such as cisplatin, 5-FU, paclitaxel, oxaliplatin and irinotecan (excluding trifluridine—tipiracil), are supported by the government. However, expensive targeted therapy and immunotherapy treatment approaches, involving agents like pembrolizumab, nivolumab, ramucirumab and T-DXd, are mostly self-funded by the patients either personally or using their personal health insurance if they have any (Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2023.102226). Typically, for expensive therapies, 70% of patients pay in full (out of their own pockets), 20% use private insurance and 10% employer/social insurance. Molecular testing is not covered by the government except for HER2 IHC, but PET—CT costs for staging and the assessment of treatment response are partially subsidised. New drugs are typically approved 1-2 years after their EMA/FDA approvals and are available 3-4 weeks after Malaysian approval. The biggest limiting factor to accessing new treatments and new diagnostic tests is cost, with a limited budget allocated to the Ministry of Health and Ministry of Education (teaching) hospitals per year for tests and treatment. In private centres, patients use either their own health insurance or out-of-pocket funding if they do not have insurance.

PSMO

The Philippines comprises over 7000 islands with a range of different procurement policies. However, specialised cancer care is focussed in urbanised areas. Access to cancer drugs and novel treatments in the Philippines first requires PFDA approval and then inclusion in the Philippine National Drug Formulary, permitting access to them in government centres. However, not all PFDA-approved drugs are in the National Drug Formulary. Most laboratory tests and diagnostics are available in the big cities like Manila and in big treatment centres; thus, 'availability for all patients' is an issue. For example, in terms of diagnostic tests, HER2 IHC testing is accessible over the entire country but not all centres can carry out *in situ* hybridisation testing. MSI/dMMR testing is approved but few centres can carry out the tests, and germline testing has to be carried out overseas. Also, not all cancer centres have access to PET—CT facilities which are restricted to private hospitals and some government hospitals. Most of the drugs cited in the recommendations above (Supplementary Table S11, available at https://doi.org/10.1016/j.esmoop.2023.102226) are available in the Philippines, although not reimbursed resulting in 100% out-of-pocket patient payments. For example, trastuzumab is approved for breast cancer but not GC. Nivolumab in combination with ChT is not approved by the PFDA so there is no local access to the drug. Pembrolizumab, ramucirumab and trifluridine—tipiracil are approved by the PFDA but are not in the National Drug Formulary. T-DXd is not PFDA approved and is not commercially available. Some agents can be obtained for compassionate use from Hong Kong or Singapore. Thus, the biggest limiting factor for access to optimal cancer care is cost, resulting in limited diagnostic and treatment facilities, limited PFDA drug approvals and inclusions in the National Drug Formulary, resulting in the costs of newer diagnostic tests and newer therapies being met by the patient.

SSO

Singapore has a co-payment health system utilising mandatory personal medical savings and government insurance, supplemented by private insurance and patient out-of-pocket payment of costs. Treatment in Singapore is subsidised by the government to reduce the cost to patients, but all patients have to co-pay. There is no reimbursement system. Standard diagnostic tests are covered by government insurance and personal medical savings for all patients. With regard to treatment, all Singaporeans have mandatory medical savings and government insurance. Seventy percent of Singaporeans have private insurance policies (personal and employer) which cover 90% of the out-of-pocket costs after deducting government insurance and personal medical savings. The remaining 10% of out-of-pocket costs are covered by additional insurance schemes in two in three private insurance policies. Approved drugs have to have undergone a cost-effectiveness assessment before they are put on the Cancer Drug List (CDL), and a full evaluation of new drugs can take up to 270 days. Only drugs listed on the CDL are eligible for subsidy (variable) and can be paid for using government insurance, private insurance and personal medical savings accounts. The costs of approved drugs not on the CDL are partially covered by private insurance. The limiting factors in relation to accessing new treatments in Singapore are the cost of the drugs, and the time taken for the cost—benefit analyses to be done so that the drugs can be added to the CDL. Similarly, the biggest limiting factor in relation to accessing new diagnostic tests and tools is cost, for example, if the tests involve DNA or RNA sequencing.

TOS

In Taiwan, 100% of the population (including overseas Taiwanese) are covered by NHI. The monthly payments out of pocket for NHI are relatively low. For example, the monthly out-of-pocket payment for NHI for a medical doctor in Taiwan is '5% or less' of that made by a medical doctor in Korea (personal communication). The financial coverage for reimbursement by NHI in Taiwan is basically 'all-or-none' (Supplementary Table S12, available at https://doi.org/10.1016/j.esmoop.2023.102226). The financial burden is huge and expected to increase further in the era of immuno-oncology and precision medicine. Therefore, despite approval by the Taiwan FDA which is largely a scientific evaluation based on the design and results of the individual pivotal trials, reimbursement is based on cost-effectiveness, the availability of other medications for the same indication and future budget burden. This explains the relatively limited reimbursement of expensive biologics (e.g. full reimbursement for first-line trastuzumab but not for second-line ramucirumab). In addition, the full reimbursement of second-line docetaxel for metastatic GC and full reimbursement of third-line trifluridine—tipiracil (TAS-102) for metastatic GC are covered by the NHI. Between 20% and 30% of GC patients pay for their treatment in full out of their own pockets, 10%-15% through private insurance and 0%-1% of patients through employers' insurance. Most new technology-based tests (e.g. NGS), and some of the newer therapies (e.g. immune checkpoint inhibitors in all lines of GC) are not on the NHI list for reimbursement. All GC patients pay for diagnostic tests in full (out of their own pocket) except for HER2 IHC. There is no co-payment system for either diagnostic tests or treatment. The biggest limiting factor with regard to accessing the newer treatment therapies and diagnostic tests in Taiwan is therefore the necessity for patient out-of-pocket payment.

TSCO

The public health care system in Thailand comprises three schemes: the government-based Civil Servant Medical Benefit Scheme (CSMBS; since 1975), the non-government-employed Social Security Scheme (SSS; since 1990) and the-rest-of-population-insured Universal Coverage (UC; since 2002). The majority of Thai people were covered by the UC and the SSS. All government employees and their dependents are covered by the CSMBS. All Thai GC patients are supported for their treatment costs according to the reimbursement protocol of each health care system they belong to. At present, the reimbursement policy of each scheme is on an 'all-or-none' basis, without an option for 'co-payment' (Supplementary Table S13, available at https://doi.org/10.1016/j.esmoop.2023.102226). Most novel biological or diagnostic tests (e.g. NGS and PET—CT), and the high-cost emerging therapies (e.g. anti-HER2 therapy and immune checkpoint inhibitors) are not reimbursable. The limitations of the reimbursement policy (schemes) to permit access to the high-cost, new diagnostic tests and treatments remain the biggest challenges in countries with limited resources, including Thailand.

The ESMO-MCBSs for the different systemic therapy options and new therapy combinations for the treatment of patients with GC are to be found at:

https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards?mcbs_score_cards_form%5BsearchText%5D=&mcbs_score_cards_form%5Btumour-type%5D=3&mcbs_score_cards_form%5Btumour-sub-type%5D=Gastric+or+gastroesophageal+junction+adenocarcinoma

CONCLUSIONS

The results of the voting by the Asian experts both before and after the face-to-face meeting in Tokyo showed >80% concordance with the ESMO recommendations for the treatment of patients with GC[5,17] (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.102226). Following the 'face-to-face' discussions, revisions were made to the wording of 'recommendations 3c (divided into two statements), 5a, b, c and d, 6f, 7c, 7f, 8c (renumbered to 8b), 13b and 15b' (Table 1) and 'recommendations 4c and 8b' deleted, resulting in a 100% consensus being achieved in terms of 'acceptability' for all the recommendations listed in Table 1. These recommendations therefore constitute the consensus clinical practice guidelines for the treatment of patients with GC in Asia. The variations in the availability for the patients of diagnostic testing, drugs and therefore treatment possibilities, between the different regions represented, reflect the differences in the organisation of their health care systems and their reimbursement strategies, and will have a significant impact on the implementation of the scientific recommendations in certain of these regions. Thus, policy initiatives are advised, based on this guideline document, in order to improve the access of all GC patients across all the Asian regions represented to state-of-the-art cancer care where possible, whilst recognising the constraints imposed by the heterogeneous socioeconomic situations of the different regions.

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
2. Ferlay J, Ervik M, Lam F, et al. *Global Cancer Observatory: Cancer Today*. International Agency for Research on Cancer. Available at https://gco.iarc.fr/. Accessed January 31, 2024.
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. Matsuno K, Ishihara R, Ohmori M, et al. Time trends in the incidence of esophageal adenocarcinoma, gastric adenocarcinoma, and superficial esophagogastric junction adenocarcinoma. *J Gastroenterol*. 2019;54(9):784-791.
5. Lordick F, Carneiro F, Cascinu S, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2022;33(10):1005-1020.
6. Rustgi SD, Ching CK, Kastrinos F. Inherited predisposition to gastric cancer. *Gastrointest Endosc Clin N Am*. 2021;31(3):467-487.
7. Usui Y, Taniyama Y, Endo M, et al. Helicobacter pylori, homologous-recombination genes, and gastric cancer. *N Engl J Med*. 2023;388(13):1181-1190.
8. Ang TL, Fock KM. Clinical epidemiology of gastric cancer. *Singapore Med J*. 2014;55(12):621-628.
9. Yang L, Kartsonaki C, Yao P, et al. The relative and attributable risks of cardia and non-cardia gastric cancer associated with Helicobacter pylori infection in China: a case-cohort study. *Lancet Public Health*. 2021;6(12):e888-e896.
10. Lu Y, Xiao F, Wang Y, et al. Prevalence of helicobacter pylori in non-cardia gastric cancer in China: a systematic review and meta-analysis. *Front Oncol*. 2022;12:850389.
11. Lim KG, Palayan K. A review of gastric cancer research in Malaysia. *Asian Pac J Cancer Prev*. 2019;20(1):5-11.
12. Gurjeet K, Subathra S, Bhupinder S. Differences in the pattern of gastric carcinoma between north-eastern and north-western peninsular Malaysia: a reflection of Helicobacter pylori prevalence. *Med J Malaysia*. 2004;59(4):560-561.
13. Han Z, Liu J, Zhang W, et al. Cardia and non-cardia gastric cancer risk associated with Helicobacter pylori in East Asia and the West: a systematic review, meta-analysis, and estimation of population attributable fraction. *Helicobacter*. 2023;28(2):e12950.
14. Chiang TH, Chang WJ, Chen SL, et al. Mass eradication of Helicobacter pylori to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsu Islands. *Gut*. 2021;70(2):243-250.
15. Ford AC, Forman D, Hunt RH, et al. Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2014;348:g3174.

16. Liou JM, Malfertheiner P, Lee YC, et al. Screening and eradication of Helicobacter pylori for gastric cancer prevention: the Taipei global consensus. *Gut*. 2020;69(12):2093-2112.
17. Lordick F, Candia Montero L, Castelo-Branco L, et al. Ann Oncol 2022;33(10):1005-1020. ESMO Gastric Cancer Living Guideline.v1.1 ed 2023. Available at https://www.esmo.org/living-guidelines/esmo-gastric-cancer-living-guideline. Accessed January 31, 2024.
18. Choi IJ, Kim CG, Lee JY, et al. Family history of gastric cancer and helicobacter pylori treatment. *N Engl J Med*. 2020;382(5):427-436.
19. Ford AC, Yuan Y, Forman D, et al. Helicobacter pylori eradication for the prevention of gastric neoplasia. *Cochrane Database Syst Rev*. 2020;7(7):CD005583.
20. Ford AC, Yuan Y, Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer: systematic review and meta-analysis. *Gut*. 2020;69(12):2113-2121.
21. International Agency for Research on Cancer WHO. *Helicobacter pylori* eradication as a strategy for preventing gastric cancer. IARC Working Group Report. 2014;8.
22. Choi KS, Jun JK, Suh M, et al. Effect of endoscopy screening on stage at gastric cancer diagnosis: results of the National Cancer Screening Programme in Korea. *Br J Cancer*. 2015;112(3):608-612.
23. Fan X, Qin X, Zhang Y, et al. Screening for gastric cancer in China: advances, challenges and visions. *Chin J Cancer Res*. 2021;33(2):168-180.
24. Mabe K, Inoue K, Kamada T, et al. Endoscopic screening for gastric cancer in Japan: current status and future perspectives. *Dig Endosc*. 2022;34(3):412-419.
25. Japanese Gastric Cancer Association. Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition). *Gastric Cancer*. 2023;26(1):1-25.
26. Carneiro F, Fukayama M, Grabsch HI. Gastric adenocarcinoma. In: WHO Classification of Tumours Editorial Board, ed. *Digestive Stystem Tumours*. Vol 1. Lyon, France: IARC; 2019:85-95.
27. Shitara K, Lordick F, Bang YJ, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. *Lancet*. 2023;401(10389):1655-1668.
28. Shah MA, Shitara K, Ajani JA, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. *Nat Med*. 2023;29(8):2133-2141.
29. Kang YK, Yook JH, Park YK, et al. PRODIGY: a phase III study of neoadjuvant docetaxel, oxaliplatin, and S-1 plus surgery and adjuvant S-1 versus surgery and adjuvant S-1 for resectable advanced gastric cancer. *J Clin Oncol*. 2021;39(26):2903-2913.
30. Yoshida K, Yasufuku I, Terashima M, et al. International retrospective cohort study of conversion therapy for stage IV gastric cancer 1 (CONVO-GC-1). *Ann Gastroenterol Surg*. 2022;6(2):227-240.
31. Hosogi H, Shinohara H, Tsunoda S, et al. Staging laparoscopy for advanced gastric cancer: significance of preoperative clinicopathological factors. *Langenbecks Arch Surg*. 2017;402(1):33-39.
32. Irino T, Sano T, Hiki N, et al. Diagnostic staging laparoscopy in gastric cancer: a prospective cohort at a cancer institute in Japan. *Surg Endosc*. 2018;32(1):268-275.
33. Miki Y, Tokunaga M, Tanizawa Y, et al. Staging laparoscopy for patients with cM0, type 4, and large type 3 gastric cancer. *World J Surg*. 2015;39(11):2742-2747.
34. Yamagata Y, Amikura K, Kawashima Y, et al. Staging laparoscopy in advanced gastric cancer: usefulness and issues requiring improvement. *Hepatogastroenterology*. 2013;60(124):751-755.
35. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355(1):11-20.
36. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol*. 2011;29(13):1715-1721.
37. Zhang X, Liang H, Li Z, et al. Perioperative or postoperative adjuvant oxaliplatin with S-1 versus adjuvant oxaliplatin with capecitabine in patients with locally advanced gastric or gastro-oesophageal junction adenocarcinoma undergoing D2 gastrectomy (RESOLVE): an open-label, superiority and non-inferiority, phase 3 randomised controlled trial. *Lancet Oncol*. 2021;22(8):1081-1092.
38. Zhang X, Li Z, Liang H, et al. Overall survival of perioperative or postoperative adjuvant oxaliplatin with S-1 versus adjuvant oxaliplatin with capecitabine in locally advanced gastric or gastro-oesophageal junction adenocarcinoma undergoing D2 gastrectomy: an updated analysis of RESOLVE trial. *Ann Oncol*. 2023;34(10):LBA 78.
39. Kang Y-K, Kim H-D, Yook JH, et al. Neoadjuvant docetaxel, oxaliplatin, and s-1 plus surgery and adjuvant s-1 for resectable advanced gastric cancer: final survival outcomes of the randomized phase 3 PRODIGY trial. *J Clin Oncol*. 2023;41:4067.
40. Iwasaki Y, Terashima M, Mizusawa J, et al. Gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer (JCOG0501): an open-label, phase 3, randomized controlled trial. *Gastric Cancer*. 2021;24(2):492-502.
41. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer*. 2021;24(1):1-21.
42. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet*. 2019;393(10184):1948-1957.
43. Janjigian YY, Al-Batran SE, Wainberg ZA, et al. Pathological complete response (pCR) to durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) in resectable gastric and gastro-esophageal junction cancer (GC/GEJC): interim results of the global, phase III MATTERHORN study. *Ann Oncol*. 2023;34:S1315-S1316 (LBA 1373).
44. Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med*. 2007;357(18):1810-1820.
45. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet*. 2012;379(9813):315-321.
46. Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15(12):1389-1396.
47. Yoshida K, Kodera Y, Kochi M, et al. Addition of docetaxel to oral fluoropyrimidine improves efficacy in patients with stage iii gastric cancer: interim analysis of JACCRO GC-07, a randomized controlled trial. *J Clin Oncol*. 2019;37(15):1296-1304.
48. Eom SS, Choi W, Eom BW, et al. A comprehensive and comparative review of global gastric cancer treatment guidelines. *J Gastric Cancer*. 2022;22(1):3-23.
49. Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group & Review Panel. Korean Practice Guideline for Gastric Cancer 2018: an evidence-based, multi-disciplinary approach. *J Gastric Cancer*. 2019;19(1):1-48.
50. Park SH, Lim DH, Sohn TS, et al. A randomized phase III trial comparing adjuvant single-agent S1, S-1 with oxaliplatin, and postoperative chemoradiation with S-1 and oxaliplatin in patients with node-positive gastric cancer after D2 resection: the ARTIST 2 trial. *Ann Oncol*. 2021;32(3):368-374.
51. Yu Y, Zhang Z, Meng Q, et al. Efficacy of different number of XELOX or SOX chemotherapy cycles after D2 resection for stage III gastric cancer. *J Gastric Cancer*. 2022;22(2):107-119.
52. Zaanan A, Bouche O, de la Fouchardiere C, et al. 5-Fluorouracil and oxaliplatin with or without docetaxel in the first-line treatment of HER2 negative locally advanced (LA) unresectable or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma (GASTFOX-PRODIGE 51): a randomized phase III trial sponsored by the FFCD. *Ann Oncol*. 2023;34:S1318 (LBA 1377).

53. 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.
54. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*. 2021;398(10294):27-40.
55. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2021;398(10302):759-771.
56. Rha SY, Oh DY, Yahez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. *Lancet*. 2023;24:1181-1185.
57. Chao J, Fuchs CS, Shitara K, et al. Assessment of pembrolizumab therapy for the treatment of microsatellite instability-high gastric or gastroesophageal junction cancer among patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 clinical trials. *JAMA Oncol*. 2021;7(6):895-902.
58. Pietrantonio F, Randon G, Di Bartolomeo M, et al. Predictive role of microsatellite instability for PD-1 blockade in patients with advanced gastric cancer: a meta-analysis of randomized clinical trials. *ESMO Open*. 2021;6(1):100036.
59. 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.
60. Janjigian YY, Kawazoe A, Bai Y, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. *Lancet*. 2023;402(10418):2197-2208.
61. 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.
62. Al-Batran SE, Homann N, Pauligk C, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: the AIO-FLOT3 trial. *JAMA Oncol*. 2017;3(9):1237-1244.
63. Kataoka K, Kinoshita T, Moehler M, et al. Current management of liver metastases from gastric cancer: what is common practice? New challenge of EORTC and JCOG. *Gastric Cancer*. 2017;20(5):904-912.
64. Bonnot PE, Lintis A, Mercier F, et al. Prognosis of poorly cohesive gastric cancer after complete cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (CYTO-CHIP study). *Br J Surg*. 2021;108(10):1225-1235.
65. Bonnot PE, Piessen G, Kepenekian V, et al. Cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for gastric cancer with peritoneal metastases (CYTO-CHIP study): a propensity score analysis. *J Clin Oncol*. 2019;37(23):2028-2040.
66. Rau B, Lang H, Königsrainer A, et al. The effect of hyperthermic intraperitoneal chemotherapy (HIPEC) upon cytoreductive surgery (CRS) in gastric cancer (GC) with synchronous peritoneal metastasis (PM): a randomized multicentre phase III trial (GASTRIPEC-I-trial). *Ann Oncol*. 2021;32(suppl 5):S1040.
67. Wagner AD, Syn NL, Moehler M, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev*. 2017;8(8):CD004064.
68. 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.
69. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2020;38(1):1-10.
70. Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med*. 2020;382(25):2419-2430.
71. van Cutsem E, Di Bartolomeo M, Smyth E, et al. Primary analysis of a phase II single-arm trial of trastuzumab deruxtecan (T-DXd) in western patients (Pts) with HER2-positive (HER2+) unresectable or metastatic gastric or gastroesophageal junction (GEJ) cancer who progressed on or after a trastuzumab-containing regimen. *Ann Oncol*. 2021;32:S1332.
72. Ku GY, Di Bartolomeo M, Smyth E, et al. Updated analysis of DESTINY-Gastric02: a phase II single-arm trial of trastuzumab deruxtecan (T-DXd) in western patients (Pts) with HER2-positive (HER2+) unresectable/metastatic gastric/gastroesophageal junction (GEJ) cancer who progressed on or after trastuzumab-containing regimen. *Ann Oncol*. 2022;33:S1100.
73. 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 Oncol*. 2018;19:1437-1448.
74. 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.
75. 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 gastro-esophageal junction. *J Clin Oncol*. 2016;34(13):1448-1454.
76. Kang Y, Kang WK, Di Bartolomeo M, et al. Randomized phase 3 ANGEL study of rivoceranib (apatinib) + best supportive care (BSC) vs placebo + BSC in patients with advanced/metastatic gastric cancer who failed _2 prior chemotherapy regimens. *Ann Oncol*. 2019;30:v851-v934.
77. Lu Z, Fang Y, Liu C, et al. Early interdisciplinary supportive care in patients with previously untreated metastatic esophagogastric cancer: a phase III randomized controlled trial. *J Clin Oncol*. 2021;39(7):748-756.
78. Sandhya L, Devi Sreenivasan N, Goenka L, et al. Randomized double-blind placebo-controlled study of olanzapine for chemotherapy-related anorexia in patients with locally advanced or metastatic gastric, hepatopancreaticobiliary, and lung cancer. *J Clin Oncol*. 2023;41(14):2617-2627.
79. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy*. 2015;47(9):829-854.
80. Cherny NI, Dafni U, Bogaerts J, et al. ESMO-magnitude of clinical benefit scale version 1.1. *Ann Oncol*. 2017;28(10):2340-2366.
81. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol*. 2018;29(9):1895-1902.
82. Zhao JJ, Yap DWT, Chan YH, et al. Low programmed death-ligand 1-expressing subgroup outcomes of first-line immune checkpoint inhibitors in gastric or esophageal adenocarcinoma. *J Clin Oncol*. 2022;40(4):392-402.
83. Yoon HH, Jin Z, Kour O, et al. Association of PD-L1 expression and other variables with benefit from immune checkpoint inhibition in advanced gastroesophageal cancer: systematic review and meta-analysis of 17 phase 3 randomized clinical trials. *JAMA Oncol*. 2022;8(10):1456-1465.