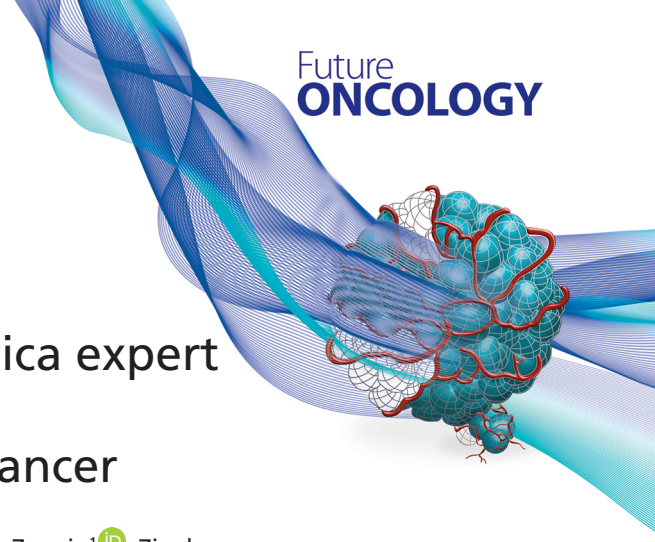
Symposium Paper

For reprint orders, please contact: reprints@futuremedicine.com

Future ONCOLOGY



The first Middle East and North Africa expert consensus recommendations for management of advanced gastric cancer

Hampig Raphael Kourie[1], Mervat Mahrous[2,3], Nabih Naim*[,1], Joseph Zouein[1], Zineb Benbrahim[4], Kakil Rasul[5], Mohsen Mokhtar[6], Ahmad Al Shehri[7], Mahmoud Shakeeb[8], Sami Khatib[9], Humaid Al-Shamsi[10], Ali Shamseddine[11] & Elisabeth Smyth[12]

[1]Hematology-Oncology Department, Saint Joseph University of Beirut, Lebanon
[2]Prince Sultan Military Medical City, Riyadh, KSA
[3]Oncology Department, Minia University, Minia, Egypt
[4]CHU Hassan II, Morocco
[5]Natonal Center for Cancer Care & Research in Hamad Medical Corporation, Doha, Qatar
[6]Director of Kasr Al Aini Oncology Unit, Cairo University, Egypt
[7]King Abdullah Medical City, Jeddah, KSA
[8]Medical City Complex, Baghdad, Iraq
[9]Secretary General of the Arab Medical Association Against Cancer, Jordan
[10]President of the Emirates Oncology Society, Burjeel Cancer Institute & VPS Healthcare, UAE
[11]Director of Gastrointestinal/Genitourinary Cancer Program at the Hematology-Oncology Division Basile Cancer Institute, American University of Beirut, Lebanon
[12]Cambridge University Hospital, NHS Foundation Trust, Cambridge, UK
*Author for correspondence: nabihnaim@gmail.com

Gastric cancer (GC) ranks as the fifth most prevalent cancer and the fourth deadliest cancer worldwide. In the Middle East and North Africa (MENA) region, GC represents about 4.8% of cancer cases with more than 35,000 new cases in 2020. To strengthen and improve the management of this cancer in the region, a group of MENA experts in the field of GC developed the first MENA consensus recommendations for the management of advanced GC. A total of 28 statements were drafted, discussed and voted on, using a modified Delphi process, during a virtual consensus meeting. The statements addressed the areas of epidemiology, biomarkers and treatment.

First draft submitted: 18 March 2023; Accepted for publication: 4 July 2023; Published online: 1 August 2023

Keywords: clinical practice guidelines • consensus • gastric cancer • MENA

According to data from GLOBOCAN 2020, gastric cancer (GC) is the fifth most prevalent cancer worldwide. It also ranks fourth in terms of cancer death with more than 768,000 deaths in 2020 [1]. In the Middle East and North Africa (MENA) region, 35,000 new cases of GC were diagnosed in 2020, accounting for about 4.8% of all cancer cases in this region. The estimated age-standardized incidence rates per 100,000 are the highest in Oman (8.0) and Yemen (7.1) and the lowest in Kuwait (2.7), Saudi Arabia (2.7) and Sudan (2.5) [1].

Adenocarcinoma represents the most common histologic type, accounting for approximately 85–95% of all GCs [2,3]. GC has a poor prognosis, especially when the diagnosis is made at an advanced stage. In fact, advanced GC has an overall survival (OS) of 3–5 months without treatment [4]. Prognosis and survival rate data for GC are rare in the MENA region. However, the data available suggest that survival rates in the MENA region are similar to European rates. According to GLOBOCAN 2020, the estimated age-standardized mortality rate for both sexes and all ages is around 5.8 in the WHO East Mediterranean Region and around 6.0 in the WHO Europe Region [1,5,6].

Clear MENA guidelines for the management of patients with advanced GC are an unmet need in the MENA region. Their development could strengthen and improve management and facilitate the fight against this burden. Therefore, a panel of MENA experts in the field of GC drafted and developed the first expert consensus recommendations for the management of advanced GC in the region.

Future Medicine

Table 1. Levels of evidence.	
I	Evidence from at least one large randomized controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with suspicion of bias (low methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies of case-control studies
V	Studies without control group, case reports and expert opinions

Methods

Twenty-eight statements on the management of advanced GC in the MENA region were drafted based on the 2022 National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline for the management of GC and on the European Society for Medical Oncology (ESMO) Clinical Practice Guideline for diagnosis, treatment and follow-up of GC [7,8]. The statements were discussed and voted on by a panel composed of several MENA experts in the field of GC during a virtual consensus meeting held on 1 September 2022.

Panel composition

A panel of MENA experts in the field of GC was selected. The panel included ten experts from eight different countries: two experts from Saudi Arabia and Lebanon, one expert each from Egypt, Qatar, the United Arab Emirates, Iraq and Morocco and a chairman-expert from the UK.

Statements

Twenty-eight statements were drafted prior to the meeting and divided into six sections. The statements were shared with the panel of experts 1 week ahead of the meeting in order to collect their comments. The first section, titled "Generalities and Epidemiology," included five statements. The second section discussed the topic of biomarkers and included seven statements. The four other sections included general statements related to treatment and management and specific statements about the management of HER2-positive and HER2-negative GC. The statements were drafted based on the 2022 NCCN Clinical Practice Guideline for the management of GC and on the ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up of GC [1,2]. Finally, the levels of evidence for the statements were added between brackets next to each statement based on a literature review and according to an adapted version of the Infectious Diseases Society of America–US Public Health Service grading system (Table 1) [9].

Discussion & voting process

A modified Delphi method was used for the discussion and voting during the consensus meeting. Votes were based on the evidence available in the medical literature and on the practices and feasibility in MENA countries. The voting was cast based on a scale from A to E where A means 'accept completely', B means 'accept with some reservations', C means 'accept with major reservations', D means 'reject with some reservations' and E means 'reject with major reservations'.

Discussion

Generalities & epidemiology

- The incidence of GC in most countries in the MENA region is relatively lower than in other parts of the world. [V] (A = 22.2%; B = 77.8%; C = 0%; D = 0%; E = 0%)
- Differentiating between GC and esophagogastric junction cancer is crucial as they may require different management in the setting of localized disease. [V] (A = 66.7%; B = 33.3%; C = 0%; D = 0%; E = 0%)
- Tumors at the esophagogastric junction with an epicenter located at >2 cm into the proximal stomach are considered gastric tumors. [V] (A = 88.9%; B = 11.1%; C = 0%; D = 0%; E = 0%)
- HER2-positive GC represents 15–20% of newly diagnosed metastatic GC, with the incidence of HER2-positive GC being concordant with international incidence. [V] (A = 88.9%; B = 11.1%; C = 0%; D = 0%; E = 0%)
- Gastric adenocarcinoma is the most common histological type with the intestinal subtype being the most prevalent [V] (A = 87.5; B = 12.5%; C = 0%; D = 0%; E = 0%)

The MENA region is regarded as a low-incidence region for GC [1]. However, there are variations in GC incidence within the MENA region with higher incidence rates being found in Oman and Yemen and lower incidence rates being found in Kuwait, Saudi Arabia and Sudan [1]. The panel reached a consensus with some reservations, due to the variation of incidence between MENA countries, since some countries have higher incidence than others. Moreover, the panel reported the issue of the lack of registry and inaccurate reporting of GC cases resulting in a lower GC incidence reported by the WHO, GLOBOCAN and other publications compared with the incidence seen in everyday practice.

As per the Eighth Edition American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) staging of cancers of the esophagus and esophagogastric junction, esophagogastric junction cancer is defined as a tumor with an epicenter that extends <2 cm into the gastric cardia [10]. The panel stresses the importance of differentiating between GC and gastroesophageal junction cancer in the early setting due to the choice of treatment between perioperative chemotherapy and chemoradiation followed by surgery [11].

The panel also expressed reservations concerning the true incidence of HER2-positive GC in the region, mainly due to the lack of publications regarding HER2 prevalence in some countries. This is mainly due to the disparities in testing for HER2 positivity in the diagnosis of GC. In fact, in some countries of the MENA region, all patients are tested for HER2 upon diagnosis, whereas, in others, due to limited testing accessibility and resources, not all patients are tested for HER2 positivity. However, based on the available studies the panel estimates that HER2-positive GC represents approximately 15–20% of all newly diagnosed GCs in the MENA region [12,13].

A consensus was reached regarding the most prevalent GC histological type. In fact, gastric adenocarcinoma is the most prevalent type [13,14]. The most prevalent subtype is the intestinal subtype at around 60% with increasing prevalence of the signet-ring cells subtype at around 30–40% [15].

The gold standard for the diagnosis of GC is an endoscopic examination along with multiple biopsies to confirm the diagnosis and determine the histological type. Endoscopic ultrasound is a useful tool to identify infiltrative regions. Furthermore, a CT scan of the abdomen and chest provides information on the presence of metastases such as in the chest, lung or peritoneum [7,16]. PET-CT is an important tool to identify metastases that were not detected by CT scan. However, it is important to note that, according to a prospective study by Smyth *et al.*, PET-CT often fails to detect metastases in mucinous or diffuse GC [17].

Biomarkers

- HER2 testing should be carried out systematically on all patients at the time of diagnosis of advanced GC. [V] (A = 88.9%; B = 11.1%; C = 0%; D = 0%; E = 0%)
- HER2 testing can be performed by immunohistochemistry (IHC) and confirmed by *in situ* hybridization if needed or by next-generation sequencing (NGS) in accredited and/or qualified laboratories. [V] (A = 88.9%; B = 0%; C = 11.1%; D = 0%; E = 0%)
- Mismatch repair testing or microsatellite instability (MSI) testing should be carried out systematically on all patients at the time of diagnosis of advanced GC. [V] (A = 100%; B = 0%; C = 0%; D = 0%; E = 0%)
- MSI testing can be performed by PCR or NGS or by testing mismatch repair using IHC in accredited and/or qualified laboratories. [V] (A = 90.0%; B = 10.0%; C = 0%; D = 0%; E = 0%)
- PD-L1 testing should be done in patients with newly diagnosed metastatic GCs who are eligible for PD-1 inhibitors treatment. [V] (A = 88.9%; B = 11.1%; C = 0%; D = 0%; E = 0%)
- *NTRK* gene fusions testing by IHC is optional in the metastatic setting. [V] (A = 70%; B = 20%; C = 10%; D = 0%; E = 0%)
- PD-L1 testing can be performed by IHC. [V] (A = 90.0%; B = 10.0%; C = 0%; D = 0%; E = 0%)

The panel reached a consensus on the fact that HER2 testing should be systematically done at the time of diagnosis of metastatic GC. Testing can be done preferentially by IHC and confirmed by *in situ* hybridization when needed. NGS is also another option for HER2 testing. However, the turnover time for NGS is longer and the technique is not widely available, making IHC the cheaper and faster method for testing. The panel acknowledges that NGS is routinely done for all patients in some institutions but the lack of multiple targeted therapies in GC, as opposed to lung cancer, makes NGS not useful in the clinical setting, especially since NGS is not yet validated as a predictive tool for the benefit of trastuzumab. However, NGS can give insight into the tumor's intrinsic mutations and is useful for research purposes.

10.2217/fon-2023-0219

The experts recommend systematic testing for mismatch repair or MSI on all patients upon diagnosing an advanced GC. This testing can be done using PCR or NGS for MSI testing or IHC for mismatch repair testing. However, some experts voiced their reservations concerning MSI/mismatch repair testing, especially that in 10% of cases, IHC results can be false due to heterogeneity and confirmatory testing using PCR must be done. Therefore, if a patient is MLH1-deficient and not responding to immunotherapy, mismatch repair testing by PCR must be done to confirm the MSI-high status found on the IHC completed upon diagnosis.

The panel agrees that PD-L1 testing along with HER2 and MSI testing are the three mandatory tests that should be done in every patient diagnosed with metastatic GC. PD-L1 testing is usually done by IHC using an US FDA-approved companion diagnostic test.

The experts recommend *NTRK* gene fusion testing as an option because of the lack of accessibility to the test, the rarity of the fusion and the absence of treatment options.

Treatment options

- The pillar for first-line advanced GC treatment is fluoropyrimidine in combination with platinum agents. [I] (A = 100%; B = 0%; C = 0%; D = 0%; E = 0%)
- Oxaliplatin is preferred over cisplatin because of its lower toxicities and better tolerability for all patients and especially for the elderly. [I] (A = 100%; B = 0%; C = 0%; D = 0%; E = 0%)

All the panel experts agree that first-line treatment of advanced GC should be based on the combination of fluoropyrimidine and platinum agents since it was shown to be more effective than fluoropyrimidine monotherapy with tolerable adverse events [18].

The experts also agree on the fact that oxaliplatin is preferred over cisplatin because of lower toxicities and better tolerability for all patients and especially for the elderly. A study comparing fluorouracil, leucovorin and oxaliplatin regimen with the fluorouracil, leucovorin and cisplatin regimen demonstrated that, in patients over 65 years old, the progression-free survival (PFS) and OS were better with oxaliplatin compared with cisplatin (PFS: 6.0 vs 3.1 months; OS: 13.9 vs 7.2 months). However, it should be noted that treatment with oxaliplatin is associated with neuropathy [19].

Concerning the surgical management of advanced GC, the ESMO guidelines do not recommend gastrectomy for the management of metastatic GC, unless it is required as a palliative treatment for symptoms [7]. In fact, in a phase 3 randomized controlled trial, gastrectomy followed by chemotherapy did not show a survival benefit compared with chemotherapy alone in oligometastatic GC without resection of metastases [20]. However, a phase 2 trial that enrolled 252 patients with advanced GC and gastroesophageal cancer reported favorable outcomes in patients with oligometastatic GC who received neoadjuvant FLOT followed by gastrectomy [21]. Several studies are currently ongoing and are exploring surgical interventions in advanced GC such as the FLOT 5-RENAISSANCE trial and the SURGIGAST study [22,23]. The data from these trials may be useful to better understand the efficacy and role of surgery in the setting of metastatic GC. Furthermore, 'conversion therapy' in the case of metastatic GC is becoming an important perioperative tool with favorable outcomes. Conversion therapy consists of maintaining a resectable state of oligometastatic GC or diminishing the metastasis size in order to convert an unresectable tumor to a resectable tumor. This can be achieved using a combination of chemotherapy, immunotherapy and targeted therapy [24–26].

HER2 positivity

- HER2-positive advanced gastric adenocarcinoma should be treated with trastuzumab in combination with fluoropyrimidine and platinum agents. [I] (A = 30%; B = 44.4%; C = 22.2%; D = 0%; E = 0%)
- Trastuzumab in combination with pembrolizumab, fluoropyrimidine and platinum agents is an option when available for the treatment of HER2-positive advanced gastric adenocarcinoma. [I] (A = 30%; B = 44.4%; C = 22,2%; D = 0%; E = 0%)
- Fam-trastuzumab deruxtecan-nxki (Enhertu) is a good option as a second-line treatment for patients with HER2-positive advanced adenocarcinoma having progressed on a trastuzumab-based regimen. [III] (A = 30%; B = 50%; C = 20%; D = 0%; E = 0%)
- Ramucirumab in combination with paclitaxel remains a valid option in the second-line setting for HER2-positive advanced GC. [I] (A = 100%; B = 0%; C = 0%; D = 0%; E = 0%)

- Trastuzumab is not recommended beyond progression for HER2-positive GC while trastuzumab deruxtecan may be considered in the second line and beyond. [II] (A = 100%; B = 0%; C = 0%; D = 0%; E = 0%)

The panel raised some reservations about pembrolizumab for the treatment of HER2-positive advanced gastric adenocarcinoma due to the lack of clear data regarding the OS and the inequality in pembrolizumab access in this setting. Furthermore, the panel raised the issue that the addition of pembrolizumab to trastuzumab and chemotherapy is not yet approved by EMA. However, the panel acknowledges that approximately 85% of HER2-positive GCs are PD-L1-positive, making GC an immuno-sensitive tumor [27]. Therefore, the experts believe that with such positivity of PD-L1, the addition of pembrolizumab could be beneficial, however, with the lack of studies that prove survival benefit, the addition of pembrolizumab to trastuzumab and chemotherapy remains an option to be confirmed.

Fam-trastuzumab deruxtecan-nxki efficacy in the second-line treatment of patients with HER2-positive advanced GC was studied in two phase II trials. The first study on an Asian population that did not require a biopsy for HER2 testing after progression showed an objective response rate (ORR) of 51% with a median OS of 12.5 months in comparison with 8.4 months for chemotherapy [28]. The second study on a Western population required a biopsy for HER2 testing after progression and showed an ORR of 38% with a median PFS of 5.4 months [29]. The latter study was nonrandomized. The panel insists on the necessity of non-Asian randomized data studying the efficacy of fam-trastuzumab deruxtecan in the second line and comparing it with ramucirumab in the second line. The panel, therefore, considers fam-trastuzumab deruxtecan as a valid option in the second line with some reservations mainly due to insufficient data as more studies are required to assess its true efficacy especially compared with ramucirumab and the need for HER2 retesting after first-line progression.

The experts reached a consensus regarding the use of ramucirumab in combination with paclitaxel in the second line for HER2-positive advanced GC. Ramucirumab alone remains a valid option for patients that are not suitable to receive either fam-trastuzumab deruxtecan or chemotherapy since it is associated with a low toxicity profile that would especially benefit frail patients. Regarding trastuzumab, the panel agrees that it is not recommended beyond progression for HER2-positive GC. However, trastuzumab deruxtecan may be considered in the second line and beyond.

HER2 negativity

- Doublet chemotherapy is preferred over triplet chemotherapy. [V] (A = 100%; B = 0%; C = 0%; D = 0%; E = 0%)
- HER2-negative advanced gastric adenocarcinoma should be treated with fluoropyrimidine and platinum agents in the first-line setting. [I] (A = 100%; B = 0%; C = 0%; D = 0%; E = 0%)
- Nivolumab in combination with chemotherapy is the standard of care in HER2-negative advanced gastric carcinoma with a Combined Positive Score (CPS) $\geq$ 5. [I] (A = 90%; B = 10%; C = 0%; D = 0%; E = 0%)
- Ramucirumab single agent or in combination with paclitaxel is recommended as a second-line therapy in patients with HER2-negative advanced gastric adenocarcinoma. [I] (A = 100%; B = 0%; C = 0%; D = 0%; E = 0%)
- When ramucirumab is not available, single-agent paclitaxel, docetaxel or irinotecan is a valid option or FOLFIRI. [II] (A = 100%; B = 0%; C = 0%; D = 0%; E = 0%)
- Trifluridine in combination with tipiracil is an option for third-line or subsequent therapy [I] (A = 75%; B = 25%; C = 0%; D = 0%; E = 0%)

The panel recommends the use of doublet chemotherapy rather than a triplet regimen for the first-line treatment of HER2-negative GC. Triplet regimens should only be used in some circumstances such as an oligometastatic disease in a fit patient. Furthermore, the preferred doublet therapy for the first-line treatment of HER2-negative GC is a fluoropyrimidine and platinum agents combination.

Nivolumab in combination with chemotherapy is currently FDA-approved for metastatic GC regardless of CPS score [30]. However, the NCCN guidelines do not recommend treating all patients with HER2-negative advanced GC with nivolumab, only those with a CPS $\geq$5, because of the lack of data for CPS <5. Moreover, the panel insists that the NCCN recommendation for nivolumab with a CPS $\geq$5 is classified as level I evidence whereas the CPS <5 is classified as IIb [8]. Although common practice in the USA is to treat all patients with HER2-negative advanced GC with nivolumab in combination with chemotherapy the panel recommends a more restrictive use of nivolumab with only a CPS $\geq$5 in the MENA region. This is because nivolumab given in patients regardless of

PD-L1 status was associated with a better PFS (10.45 vs 8.34 months) but no improvement in OS [31]. Finally, the panel raised the issue concerning CPS <5, which should be subdivided into CPS <1 and CPS = 0 and be further studied. For patients with a CPS <5, the experts recommend treatment with first-line chemotherapy.

The panel recommends ramucirumab in combination with paclitaxel in the second line for patients with HER2-negative advanced GC. The experts also agree that although ramucirumab monotherapy is an option in this setting, it is usually rarely used.

The experts discussed the use of 5-FU, leucovorin and irinotecan (FOLFIRI) after FLOT since it is associated with an ORR of 29% [25,26]. The panel also considers paclitaxel, docetaxel and irinotecan monotherapy as valid options [32,33].

The panel acknowledges that few patients get to the third line. Trifluridine in combination with tipiracil showed an improved median OS of 5.7 months versus 3.6 months for the placebo in the third line [34]. Therefore, the panel reached a consensus on trifluridine in combination with tipiracil being an option for third-line or subsequent-line therapy for patients with advanced GC. However, some reservations were expressed by some experts given that the response rate, PFS and OS with this therapy are quite low. The panel also pointed out that FOLFIRI is also an option in the third line based on the Japanese experience where a third of the patients reach the third line [35].

Other recommendations

- Pembrolizumab and dostarlimab are recommended options for the treatment of patients with MSI-high/deficient mismatch repair advanced GC who have progressed following prior treatment and with no satisfactory alternative treatment options. It can also be considered in the first-line setting if available. [III] (A = 75%; B = 25%; C = 0%; D = 0%; E = 0%)
- For patients with Microsatellite Stable Tumors with High Mutational Burden (MSS TMB-H) >10 non-POLE gastric tumors who have progressed following prior treatment, who have no satisfactory alternative treatment options and who have not previously been exposed to immune checkpoint inhibitors, pembrolizumab is a good option. [IV] (A = 33.3%; B = 66.7%; C = 0%; D = 0%; E = 0%)
- Entrectinib or larotrectinib are recommended for *NTRK* gene fusion-positive gastric tumors in second-line or subsequent therapy. [III] (A = 88.9%; B = 11.1%; C = 0%; D = 0%; E = 0%)

The panel agrees that pembrolizumab is an option for patients with MSI-high advanced GC having progressed on prior regimens. In fact, Keynote-059 demonstrated an ORR of 11.6% and a median duration of response of 8.4 months [36]. Dostarlimab is now approved for all deficient mismatch repair advanced solid tumors with an ORR of 41.6% with a tolerable safety profile making it an option for the treatment of MSI-high/deficient mismatch repair advanced GC [28,29]. Although the panel recognizes the efficacy and usefulness of dostarlimab in this setting, the unavailability of the drug in the MENA region until now is an obstacle to its use in this setting. Finally, the panel agrees that in the presence of an MSI-high advanced GC, treatment with an anti-PD-1 should be favored in the first line, if available.

The panel remains skeptical about the efficacy of pembrolizumab in patients with TMB-H >10. In fact, a study assessing the association of TMB with pembrolizumab efficacy as a first-line therapy in patients from Keynote-062 found that 44% of patients with a TMB-H >10 were also MSI-high. After the exclusion of MSI-high patients, the efficacy of pembrolizumab in patients with only TMB-H >10 decreased [37]. The panel also raised some issues about the cutoff for defining a high TMB.

The experts agree completely or with some reservation that entrectinib or larotrectinib should be given to patients with *NTRK* gene fusion-positive advanced GC who have progressed on prior treatment regimens.

It is important to note that many novel molecules and strategies are currently being investigated for the management of advanced GC. In recent years, there has been increased interest in studying antibody–drug conjugates for the treatment of GC. In fact, several new antibody–drug conjugates targeting receptors such as EGFR, HER2, HER3 or claudin 18.2 are now being investigated with encouraging preliminary results [38]. For instance, in a recent phase 1 trial, a claudin 18.2 antibody–drug conjugate (CMG901) demonstrated promising results in eight patients with claudin 18.2-positive GC (ORR = 75%; disease control rate = 100%) [39]. Larger trials investigating this molecule are currently enrolling [40].

Furthermore, the panel discussed the importance of supportive care in the management of patients with advanced GC. In fact, despite all the development in the field of chemotherapy and targeted therapies, the prognosis of GC remains unsatisfactory. Special attention should be given to nutritional care, given the fact that malnutrition is

particularly prevalent in this group of patients. A nutritional assessment should be done at the time of diagnosis and nutritional status should be followed regularly to detect any signs of malnutrition as soon as possible and to enable early multidisciplinary intervention [41]. Finally, regular follow-up for patients with advanced GC is important to detect disease progression as early as possible and to readapt the treatment, if possible. Follow-up should include regular visits with a complete history and physical exam every 3 to 6 months for the first 2 years, then every 6 to 12 months for the following 3 years and then annually. Blood tests should be ordered when indicated. A CT scan with IV contrast for the chest, abdomen and any area of interest should be obtained every 6 to 12 months for the first 2 years and then annually for 5 years [7,8].

Conclusion

A panel of MENA experts in the field of GC drafted and issued the first consensus recommendations directed specifically at the management of patients with advanced GC in the MENA region. The experts reached a consensus on key elements related to epidemiology, biomarkers and treatment of advanced GC. A high level of agreement was reached for the majority of the statements. The 28 statements along with their level of evidence and percentage of agreement are summarized in Supplementary Table 1.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2023-0219

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as: •• of considerable interest

1. WHO GLOBOCAN. Cancer today http://gco.iarc.fr/today/home (Accessed 18 January 2023).
2. Chang JS, Kuo SH, Chu PY *et al*The epidemiology of gastric cancers in the era of *Helicobacter pylori* eradication: a nationwide cancer registry-based study in Taiwan. *Cancer Epidemiol. Biomarkers Prev.* 28(10), 1694–1703 (2019).
3. Waddell T, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 24 (Suppl. 6), vi57–vi63 (2013).
4. Hu HM, Tsai HJ, Ku HY *et al.*Survival outcomes of management in metastatic gastric adenocarcinoma patients. *Sci. Rep.* 11(1), 23142 (2021).
5. Al-Moundhri MS, Al-Bahrani B, Burney IA et *al.* The prognostic determinants of gastric cancer treatment outcome in Omani Arab patients. *Oncology* 70(2), 90–96 (2006).
6. Bani-Hani KE, Yaghan RJ, Heis HA *et al.* Gastric malignancies in Northern Jordan with special emphasis on descriptive epidemiology. *World J. Gastroenterol.* 10(15), 2174–2178 (2004).
7. Lordick F, Carneiro F, Cascinu S *et al.* Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann. Oncol.* 33(10), 1005–1020 (2022).

•• **The statements drafted for this consensus were based on this European Society for Medical Oncology Clinical Practice Guideline.**

8. Ajani JA, D'Amico TA, Bentrem DJ *et al.* Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J. Natl Compr. Cancer Netw.* 20(2), 167–192 (2022).

•• **The statements drafted for this consensus were based on the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (gastric cancer).**

9. Dykewicz CA. Centers for Disease Control and Prevention, Infectious Diseases Society of America, American Society of Blood and Marrow Transplantation. Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. *Clin. Infect. Dis.* 33(2), 139–144 (2001).
10. Rice TW, Patil DT, Blackstone EH. 8th Edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. *Ann. Cardiothorac. Surg.* 6(2), 119–130 (2017).
11. Ge XL, Liu S, Zhu HC *et al.* Survival benefit of neoadjuvant radiation therapy in patients with carcinoma of gastroesophageal junction and distal esophagus? A population-based study. *Transl. Cancer Res.* 6(2), (2017). https://tcr.amegroups.com/article/view/13156

12. Assi T, El Rassy E, Khazzaka A *et al.* Characteristics of gastric cancer in Lebanon: a descriptive study from a single institutional experience. *J. Gastrointest. Cancer* 49(1), 21–24 (2018).
13. Kattan J, el Karak F, Farhat F *et al.* Prevalence of Her2-neu status and its clinicopathological association in newly diagnosed gastric cancer patients. *BMC Cancer* 22, 1114 (2022).
14. Antoine AR, Joyce S, Joanna S, Christine K, Khoury Salem E, Philippe S. Gastrointestinal cancer characteristics in Lebanon. *Arab J. Gastroenterol.* 23(1), 52–57 (2022).
15. Al-Shamsi HO. Clinicopathological features of gastric cancer in a cohort of Gulf Council countries' patients: a cross-sectional study of 96 cases. *J. Oncol. Res. Rev. Rep.* 2(3), 1–3 (2021).
16. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. *Lancet* 396(10251), 635–648 (2020).
17. Smyth E, Schöder H, Strong VE *et al.* A prospective evaluation of the utility of 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography and computed tomography in staging locally advanced gastric cancer. *Cancer* 118(22), 5481–5488 (2012).
18. Arai H, Iwasa S, Boku N *et al.* Fluoropyrimidine with or without platinum as first-line chemotherapy in patients with advanced gastric cancer and severe peritoneal metastasis: a multicenter retrospective study. *BMC Cancer* 19(1), 652 (2019).
19. Al-Batran SE, Hartmann JT, Probst S *et al.* Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J. Clin. Oncol.* 26(9), 1435–1442 (2008).
20. 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.* 17(3), 309–318 (2016).
21. 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.* 3(9), 1237–1244 (2017).
22. Al-Batran SE, Goetze TO, Mueller DW *et al.* The RENAISSANCE (AIO-FLOT5) trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction–a phase III trial of the German AIO/CAO-V/CAOGI. *BMC Cancer* 17(1), 893 (2017).
23. ClinicalTrials.gov. Surgical resection plus chemotherapy versus chemotherapy alone in oligometastatic stage IV gastric cancer. https://clinicaltrials.gov/ct2/show/NCT03042169 (Accessed 29 June 2023).
24. Chevallay M, Wassmer CH, Iranmanesh P, Jung MK, Mönig SP. Multimodal treatment in oligometastatic gastric cancer. *World J. Gastrointest. Oncol.* 14(2), 434–449 (2022).
25. Morgagni P, Solaini L, Framarini M *et al.* Conversion surgery for gastric cancer: a cohort study from a western center. *Int. J. Surg.* 53, 360–365 (2018).
26. Yasufuku I, Nunobe S, Ida S *et al.* Conversion therapy for peritoneal lavage cytology-positive type 4 and large type 3 gastric cancer patients selected as candidates for R0 resection by diagnostic staging laparoscopy. *Gastric Cancer* 23(2), 319–327 (2020).
27. Lian J, Zhang G, Zhang Y *et al.* PD-L1 and HER2 expression in gastric adenocarcinoma and their prognostic significance. *Dig. Liver Dis.* 54(10), 1419–1427 (2022).
28. Shitara K, Bang YJ, Iwasa S *et al.* Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N. Engl. J. Med.* 382(25), 2419–2430 (2020).
29. van Cutsem E, Bartolomeo MD, Smyth E *et al.* LBA55 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.* 32, S1332 (2021).
30. US FDA. FDA approves nivolumab in combination with chemotherapy for metastatic gastric cancer and esophageal adenocarcinoma (2021). www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-combination-chemotherapy-metastatic-gastric-cancer-and-esophageal (Accessed 29 June 2023).
31. Kang YK, Chen LT, Ryu MH *et al.* Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 23(2), 234–247 (2022).
32. Hironaka S, Ueda S, Yasui H *et al.* Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. *J. Clin. Oncol.* 31(35), 4438–4444 (2013).
33. Ford HER, Marshall A, Bridgewater JA *et al.* Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol.* 15(1), 78–86 (2014).
34. 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.* 19(11), 1437–1448 (2018).
35. Erdem GU, Bozkaya Y, Ozdemir NY, Demirci NS, Yazici O, Zengin N. 5-Fluorouracil, leucovorin, and irinotecan (FOLFIRI) as a third-line chemotherapy treatment in metastatic gastric cancer, after failure of fluoropyrimidine, platinum, anthracycline, and taxane. *Bosn. J. Basic Med. Sci.* 18(2), 170–177 (2018).

36. Fuchs CS, Doi T, Jang RW *et al.* Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. *JAMA Oncol.* 4(5), e180013 (2018).

37. Lee KW, Van Cutsem E, Bang YJ *et al.* Association of tumor mutational burden with efficacy of pembrolizumab±chemotherapy as first-line therapy for gastric cancer in the phase III KEYNOTE-062 study. *Clin. Cancer Res.* 28(16), 3489–3498 (2022).

38. Zhu Y, Zhou M, Kong W, Li C. Antibody-drug conjugates: the clinical development in gastric cancer. *Front. Oncol.* 13, 1211947 (2023).

39. Xu R-H, Wei X, Zhang D *et al.* A phase 1a dose-escalation, multicenter trial of anti-claudin 18.2 antibody drug conjugate CMG901 in patients with resistant/refractory solid tumors. *JCO* 41(Suppl. 4), 352 (2023).

40. ClinicalTrials.gov Safety, tolerability, pharmacokinetics, and preliminary efficacy, phase 1 study of CMG901. https://clinicaltrials.gov/ct2/show/NCT04805307 (Accessed 29 June 2023).

41. Mizukami T, Piao Y. Role of nutritional care and general guidance for patients with advanced or metastatic gastric cancer. *Future Oncol.* 17(23), 3101–3109 (2021).

10.2217/fon-2023-0219