Gastric Cancer, Version 2.2022

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ABSTRACT

Gastric cancer is the third leading cause of cancer-related deaths worldwide. Over 95% of gastric cancers are adenocarcinomas, which are typically classified based on anatomic location and histologic type. Gastric cancer generally carries a poor prognosis because it is often diagnosed at an advanced stage. Systemic therapy can provide palliation, improved survival, and enhanced quality of life in patients with locally advanced or metastatic disease. The implementation of biomarker testing, especially analysis of HER2 status, microsatellite instability (MSI) status, and the expression of programmed death-ligand 1 (PD-L1), has had a significant impact on clinical practice and patient care. Targeted therapies including trastuzumab, nivolumab, and pembrolizumab have produced encouraging results in clinical trials for the treatment of patients with locally advanced or metastatic disease. Palliative management, which may include systemic therapy, chemoradiation, and/or best supportive care, is recommended for all patients with unresectable or metastatic cancer. Multidisciplinary team management is essential for all patients with localized gastric cancer. This selection from the NCCN Guidelines for Gastric Cancer focuses on the management of unresectable locally advanced, recurrent, or metastatic disease.

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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Individual disclosures for the NCCN Gastric Cancer, Version 2.2022 Panel members can be found on page 192. (The most recent version of these guidelines and accompanying disclosures are available at [NCCN.org](https://www.nccn.org).)

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WORKUP

- H&P
- Upper GI endoscopy and biopsy^a
- Chest/abdomen/pelvic CT with oral and IV contrast
- FDG-PET/CT evaluation (skull base to mid-thigh) if no evidence of M1 disease^b and if clinically indicated
- CBC and comprehensive chemistry profile
- Endoscopic ultrasound (EUS) if early-stage disease suspected or if early versus locally advanced disease needs to be determined (preferred)
- Endoscopic resection (ER) is essential for the accurate staging of early-stage cancers (T1a or T1b).^c Early-stage cancers can best be diagnosed by ER.
- Biopsy of metastatic disease as clinically indicated
- Universal testing for MSI by PCR/next-generation sequencing (NGS) or MMR by IHC is recommended in all newly diagnosed patients^d
- HER2 and PD-L1 testing if metastatic adenocarcinoma is documented/suspected^{d,e}
- NGS may be considered^d
- Assess Siewert category^f
- Nutritional assessment and counseling
- Smoking cessation advice, counseling, and pharmacotherapy as indicated^g
- Screen for family history^h
- If anemia is suspected, See NCCN Guidelines for Hematopoietic Growth Factors[†]

CLINICAL STAGEⁱcTis
or
cT1aMedically fit^jNon-surgical candidate^kMedically fit,^{f,j}
potentially
resectableMedically fit,
surgically^{f,j}
unresectableNon-surgical
candidate^kLocoregional
(cM0)Stage IV
(cM1)

ADDITIONAL EVALUATION

Recommend
laparoscopy
with
cytology^lConsider
laparoscopy
with
cytology^lMultidisciplinary
review preferred^m → See GAST-2*Palliative
Management
(see GAST-9)

See Footnotes on GAST-1A

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GAST-1

Overview

The incidence of gastric cancer has decreased substantially in the United States and Western Europe over the past several decades.¹⁻⁴ However, gastric cancer still constitutes a major global health problem, especially in East Asian countries.^{5,6} Globally, there were more than 1 million cases resulting in more than 768,000 deaths in 2020, making gastric cancer the fifth most frequently diagnosed cancer and the third leading cause of cancer-related deaths in the world.^{7,8} The global incidence of gastric cancer shows wide geographic variation, with a 15- to 20-fold difference between high- and low-incidence regions.¹ The highest gastric cancer incidence rates occur in Northeast Asia, South and Central America, and Eastern Europe.^{5,6} Rates are particularly high in Japan and Korea, where gastric cancer is the most commonly diagnosed cancer in men, and in China, where gastric cancer is a leading cause of cancer-related mortality.^{5,6,9} In contrast, gastric cancer is one of the least commonly diagnosed cancers in Western Europe, sub-Saharan Africa, Australia, and North America.⁶ In the United States, an estimated 26,560 people were to be diagnosed and 11,180 people were expected to die of this

disease in 2021, making gastric cancer the 16th most commonly diagnosed cancer and the 17th leading cause of cancer-related death in the United States.^{4,10,11} Despite overall declining rates, recent evidence suggests that the incidence of early-onset gastric cancer may be rising in the United States.¹²

More than 95% of gastric cancers are adenocarcinomas, which are typically classified based on anatomic location (cardia/proximal or noncardia/distal) and histologic type (diffuse or intestinal).³ The diffuse type, which is characterized by poorly differentiated and discohesive tumor cells with a signet-ring or non-signet-ring morphology diffusely infiltrating the gastric wall in a desmoplastic stroma, is more prevalent in low-risk areas and is mostly associated with heritable genetic abnormalities.^{3,9,13-15} The intestinal type, which tends to form a mass lesion and is characterized by variably differentiated tumor cells arranged in a tubular or glandular pattern with scattered goblet cells present, occurs more frequently in high-risk areas and accounts for most of the geographic variation seen with this disease. Intestinal type gastric cancer is often related to environmental factors such as *Helicobacter pylori* infection, tobacco

FOOTNOTES FOR GAST-1

^a See Principles of Endoscopic Staging and Therapy (GAST-A*).

^b May not be appropriate for T1.

^c ER may also be therapeutic for early-stage disease/lesions.

^d See Principles of Pathologic Review and Biomarker Testing (GAST-B).

^e Tumor Epstein-Barr virus status is emerging as a potential biomarker for personalized treatment strategies for gastric cancer, but is not currently recommended for clinical care.

^f See Principles of Surgery (GAST-C*).

^g See NCCN Guidelines for Smoking Cessation†.

^h See Principles of Genetic Risk Assessment for Gastric Cancer (GAST-D*). Also see NCCN Guidelines for Colorectal Cancer Screening† and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic†.

ⁱ See Staging (ST-1*) for tumor classification.

^j Medically able to tolerate major surgery.

^k Medically unable to tolerate major surgery or medically fit patients who decline surgery.

^l Laparoscopy with cytology is performed to evaluate for peritoneal spread when considering chemoradiation or surgery. Laparoscopy with cytology is not indicated if a palliative resection is planned. Laparoscopy with cytology is indicated for clinical stage T1b or higher.

^m See Principles of Multidisciplinary Team Approach (GAST-E).

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GAST-1A

smoking, high salt intake, and other dietary factors.^{3,9,13–15} However, the role of alcohol as a risk factor for gastric cancer is without consensus. While the results of several meta-analyses have shown no appreciable association between light or moderate alcohol consumption and gastric cancer risk, they did show a positive association between heavy alcohol use and gastric cancer, particularly noncardia gastric cancer.^{16–19}

A dramatic shift in the type and location of upper gastrointestinal tract tumors has occurred in North America and Europe.^{2,20,21} There has been a marked decline in intestinal type gastric cancers of the distal stomach in North American and Western European countries over the past several decades, mainly due to enhanced access to clean drinking water, improved food preservation, an average diet with low promotion of gastric cancer, and *H pylori* eradication.^{1–4,15} However, incidence rates of diffuse type gastric cancer of the proximal stomach are rising.^{1–3} The etiology of this increase remains elusive and may be multifactorial. In contrast to the incidence trends in high income countries, tumors of the distal stomach continue to predominate in low and middle income countries.² Gastric cancer generally

carries a poor prognosis since it is often diagnosed at an advanced stage. In Japan and South Korea, where population screening is performed widely, early detection often results in improved outcomes.^{1,6} In the United States, survival rates from gastric cancer remain poor as early detection continues to pose a major challenge for health care professionals.

This selection from the NCCN Guidelines for Gastric Cancer focuses on the management of unresectable locally advanced, recurrent, or metastatic disease (to view the complete and most recent version of these Guidelines, visit NCCN.org).

Staging

The tumor (T), node (N), and metastasis (M) staging system used by the AJCC is the internationally accepted standard for cancer staging and is a major factor influencing prognosis and treatment decisions. Staging recommendations for gastric cancer presented in the eighth edition of the AJCC Cancer Staging Manual include clinical staging (cTNM; newly diagnosed, not-yet-treated patients), pathologic staging (pTNM; patients undergoing resection without prior treatment), and post

^d See Principles of Pathologic Review and Biomarker Testing (GAST-B).

^o See Principles of Systemic Therapy (GAST-F).

^p See Principles of Radiation Therapy (GAST-G*).

^{aa} See Principles of Palliative Care/Best Supportive Care (GAST-J).

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GAST-9

neoadjuvant pathologic staging (ypTNM; patients receiving preoperative therapy).²² The eighth edition also introduced modifications regarding tumors located at the esophagogastric junction (EGJ) and within the gastric cardia. Using this system, tumors involving the EGJ with an epicenter located >2 cm into the proximal stomach are now staged as gastric carcinomas. Tumors involving the EGJ with an epicenter ≤2 cm into the proximal stomach will still be staged as esophageal carcinomas. Cancers located within the gastric cardia that do not involve the EGJ are staged as gastric carcinomas.

The eighth edition of the AJCC Cancer Staging Manual provides additional resources for gastric cancer not available in the seventh edition, including the addition of new cTNM and ypTNM stage groupings, to fulfill unmet needs in staging patients under different circumstances. Due to the lack of an official clinical stage classification in the past, treating physicians have typically used the pathologic stage to clinically stage patients. Furthermore, due to the lack of yp stage groupings, pathologic staging was also applied to patients who had received preoperative therapy. The use of pathology assessments to establish cTNM and ypTNM stages has never been validated

and may not be appropriate. Therefore, new cTNM and ypTNM stage groupings and prognostic information were added to the eighth edition to overcome these issues. New clinical stage groupings and prognostic information are based on datasets from the National Cancer Database, representing patients treated surgically or non-surgically in the United States, and the Shizuoka Cancer Center dataset, representing patients treated surgically in Japan, for a total of 4,091 patients. These clinical stage groupings are different from groupings used for pathologic or post-neoadjuvant staging. The prognostic value of the newly proposed cTNM stage criteria has been externally validated in a cohort of 4,374 surgically treated gastric cancer patients in Japan.²³ Newly provided prognostic information for ypTNM staging is presented using only the 4 broad stage categories (stage I–IV) due to the limited number of patients (n=700) available for analysis. The addition of this new ypTNM stage grouping system fulfills an unmet need in the clinics because many patients with gastric cancer are now treated with preoperative therapy. Furthermore, the stage groupings and prognostic information for pTNM staging presented in the Eighth Edition are now based on data from >25,000

PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Pathologic Review
Table 1

Specimen Type	Analysis/Interpretation/Reporting ^a
Biopsy	Include in pathology report: <ul style="list-style-type: none"> • Invasion, if present • Histologic type^b • Grade • Universal testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients
Endoscopic mucosal resection	Include in pathology report: <ul style="list-style-type: none"> • Invasion, if present • Histologic type^b • Grade • Depth of tumor invasion • Vascular/lymphatic invasion • Status of mucosal and deep margins • Universal testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients
Gastrectomy, without prior chemoradiation	For pathology report, include all elements as for endoscopic mucosal resection plus <ul style="list-style-type: none"> • Location of tumor midpoint in relationship to EGJ^c • Whether tumor crosses EGJ • Lymph node status and number of lymph nodes recovered • Universal testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients, if not previously performed
Gastrectomy, with prior chemoradiation	<ul style="list-style-type: none"> • Tumor site should be thoroughly sampled for specimens s/p neoadjuvant therapy without grossly obvious residual tumor • For pathology report, include all elements as for resection without prior chemoradiation plus assessment of treatment effect

^a Use of a standardized minimum data set such as the College of American Pathologists Cancer Protocols (available at <http://www.cap.org>) for reporting pathologic findings is recommended.

^b Subclassification of gastric adenocarcinomas as intestinal or diffuse type may have implications for therapy, as intestinal type cancers may be more likely to overexpress HER2.¹

^c Midpoint of tumors arising in the proximal 2 cm of the stomach and crossing the EGJ are classified for purposes of staging as esophageal carcinomas, while those with the epicenter located greater than 2 cm into the proximal stomach are staged as gastric carcinomas.²

Continued
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GAST-B
1 OF 6

patients with gastric cancer from the International Gastric Cancer Association (IGCA) database who have had surgery with adequate lymph node removal. Patients treated with preoperative therapy were not included in the analysis. Pathologic stage groupings were refined based on 5-year survival data. Although most (84.8%) of the eligible cases from the IGCA database came from Japan and Korea, the predictive ability and accuracy of parameters used in the eighth edition for pTNM staging of gastric cancer have been validated for United States populations.^{24,25} The new pTNM staging classification criteria have also been externally validated in a cohort with a higher proportion of advanced disease than the IGCA cohort (49% had stage III disease compared with 26% in the IGCA cohort, $P < .001$).²⁶ However, limitations of this dataset still remain, including a lack of uniformity in initial clinical stage assessments, the lack of a uniform surgical approach, and the use of pTNM assessments for ypTNM staging.²²

Baseline clinical stage provides useful information for the development of an initial treatment strategy. The availability of diagnostic modalities such as endoscopic

ultrasound (EUS), CT, 18-FDG-PET/CT, and laparoscopy has greatly improved baseline clinical staging of gastric cancer.^{27–29} EUS is indicated for assessing the depth of tumor invasion (T category) as well as nodal involvement (N category).³⁰ However, the diagnostic accuracy of EUS is operator dependent, ranging from 57% to 88% for T staging and 30%–90% for N staging.³¹ In a large multi-institutional study that evaluated the use and accuracy of EUS in patients undergoing curative intent resection for gastric adenocarcinoma, the overall accuracy of EUS was 46.2% for T category and 66.7% for N category.³² Distant lymph node evaluation by EUS is also suboptimal given the limited depth and visualization of the transducer.³³ EUS may be useful for differentiating T3 and T4 tumors, but it should be used in combination with other staging modalities.^{31,32} EUS is also useful to identify superficial tumors for potential endoscopic approaches. Therefore, EUS should be used if early-stage disease is suspected or if early versus locally advanced disease needs to be determined.

CT scanning is routinely used for preoperative staging and has an overall accuracy of 43%–82% for measuring depth of invasion. In contrast, FDG-PET has a lower accuracy rate because of low FDG uptake in diffuse and

PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Assessment of Overexpression or Amplification of HER2 in Gastric Cancer

For patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach for whom trastuzumab[®] therapy is being considered, assessment for tumor HER2 overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization (ISH) method is recommended.⁴ NGS offers the opportunity to assess numerous mutations simultaneously, along with other molecular events such as amplification, deletions, tumor mutation burden, and microsatellite instability (MSI) status. NGS can be considered instead of sequential testing for single biomarkers when limited diagnostic tissue is available or when the patient is unable to undergo a traditional biopsy. The use of IHC/ISH should be considered first, followed by additional NGS testing as appropriate. Repeat biomarker testing may be considered at clinical or radiologic progression for patients with advanced/metastatic gastric adenocarcinoma.

Table 3: Immunohistochemical Criteria for Scoring HER2 Expression in Gastric Cancer^{f,g}

	Surgical Specimen Expression Pattern, Immunohistochemistry	Biopsy Specimen Expression Pattern, Immunohistochemistry	HER2 Overexpression Assessment
0	No reactivity or membranous reactivity in <10% of cancer cells	No reactivity or no membranous reactivity in any cancer cell	Negative
1+	Faint or barely perceptible membranous reactivity in ≥10% of cancer cells; cells are reactive only in part of their membrane	Cluster of five or more cancer cells with a faint or barely perceptible membranous reactivity irrespective of percentage of cancer cells positive	Negative
2+	Weak to moderate complete, basolateral, or lateral membranous reactivity in ≥10% of cancer cells	Cluster of five or more cancer cells with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Equivocal
3+	Strong complete, basolateral, or lateral membranous reactivity in ≥10% of cancer cells	Cluster of five or more cancer cells with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Positive

^e An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

^f The NCCN Guidelines Panel recommends that HER2 IHC be ordered/performed first, followed by ISH methods in cases showing 2+ (equivocal) expression by IHC.

Positive (3+) or negative (0 or 1+) HER2 IHC results do not require further ISH testing. Cases with HER2:CEP17 ratio ≥2 or an average HER2 copy number ≥6.0 signals/cell are considered positive by ISH/FISH.

^g Reprinted and adapted from Bartley AN, Washington MK, Colasacco C, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society of Clinical Pathology, and American Society of Clinical Oncology. J Clin Oncol 2017;35:446-464 with permission from the American Society of Clinical Oncology.

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GAST-B
3 OF 6

mucinous tumor types, which are common in gastric cancer.^{34,35} FDG-PET also has significantly lower sensitivity compared with CT in the detection of local lymph node involvement (56% vs 78%), although FDG-PET has improved specificity (92% vs 62%).³⁶ Thus, combined FDG-PET/CT imaging offers several potential advantages over FDG-PET or CT scans alone.³⁷ FDG-PET/CT has a significantly higher accuracy rate in preoperative staging (68%) than FDG-PET (47%) or CT (53%) alone. Additionally, reports have confirmed that FDG-PET alone is not an adequate diagnostic procedure in the detection and preoperative staging of gastric cancer, but can be helpful when used in conjunction with CT.^{38,39} FDG-PET does not take the place of staging laparoscopy given its failure to detect peritoneal disease.

Pretreatment diagnostic laparoscopy can be used to detect occult metastases. In a study conducted at Memorial Sloan Kettering Cancer Center, 657 patients with potentially resectable gastric adenocarcinoma underwent laparoscopic staging over a period of 10 years.⁴⁰ Metastatic disease (M1) was detected in 31% of patients. However, limitations of laparoscopic staging include 2-dimensional evaluation and limited use in the identification of hepatic metastases and perigastric lymph nodes.

Cytology testing of peritoneal fluid can help improve laparoscopic staging through identification of occult carcinomatosis.²⁷ Positive peritoneal cytology is associated with a poor prognosis in patients with gastric cancer and is an independent predictor for recurrence following curative resection.^{41–43} Clearing of cytology-positive disease by chemotherapy is associated with a statistically significant improvement in disease-specific survival, but cures are rare and the role of surgery is uncertain.⁴² Therefore, positive peritoneal cytology even in the absence of visible peritoneal implants should be considered as M1 disease, and surgery as initial treatment is not recommended. In patients being considered for surgical resection without preoperative therapy, laparoscopy may be useful for the detection of radiographically occult metastatic disease in patients with T3 and/or N+ tumors identified on preoperative imaging. The panel recommends performing diagnostic laparoscopy to assess the peritoneal cavity (with biopsies as needed) and cytology of peritoneal washings in medically fit patients with potentially resectable stage cT1b or higher

PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing^h

• Universal testing for MSI by polymerase chain reaction (PCR), NGS, or MMR by IHC should be performed for all newly diagnosed gastric cancers.⁵ The testing is performed on formalin-fixed, paraffin-embedded (FFPE) tissue and results are interpreted as MSI-high (MSI-H) or mismatch repair-deficient (dMMR) in accordance with CAP DNA Mismatch Repair Biomarker Reporting Guidelines.⁶ Testing should be performed only in CLIA-approved laboratories. Patients with MSI-H or dMMR tumors may be referred to a genetics counselor for further assessment in the appropriate clinical context.

MMR Interpretation

- ◊ No loss of nuclear expression of MMR proteins: No evidence of dMMR (low probability of MSI-H)
- ◊ Loss of nuclear expression of one or more MMR proteins: dMMR

MSI Interpretation

- ◊ MSI-Stable (MSS)
- ◊ MSI-Low (MSI-L)
 - 1%–29% of the markers exhibit instability
 - 1 of the 5 National Cancer Institute (NCI) or mononucleotide markers exhibits instability
- ◊ MSI-H
 - ≥30% of the markers exhibit instability
 - 2 or more of the 5 NCI or mononucleotide markers exhibit instability

PD-L1 Testing

- PD-L1 testing may be considered on locally advanced, recurrent, or metastatic gastric carcinomas in patients who are candidates for treatment with PD-1 inhibitors. An FDA-approved companion diagnostic test should be used on FFPE tissue as an aid in identifying patients for treatment with PD-1 inhibitors. PD-L1 testing should be performed only in CLIA-approved laboratories.
- Assessment of PD-L1 Protein Expression in Gastric Cancers

This is a qualitative immunohistochemical assay using anti-PD-L1 antibodies for the detection of PD-L1 protein in FFPE tissues from gastric adenocarcinoma. A minimum of 100 tumor cells must be present in the PD-L1-stained slide for the specimen to be considered adequate for PD-L1 evaluation. A specimen is considered to have PD-L1 expression if the combined positive score (CPS) ≥1. CPS is the number of PD-L1 staining cells (ie, tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.

^h PCR/NGS for MSI and IHC for MMR proteins measure different biological effects caused by dMMR function.

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GAST-B
4 OF 6

locoregional disease when considering preoperative chemoradiation and/or surgery.⁴⁰ Laparoscopy with cytology can be considered for medically fit patients with surgically unresectable disease.

In most countries, where screening programs for early detection of gastric cancer are not in use or practical because of low incidence, diagnosis is often made late in the disease course. Approximately 50% of patients present with advanced disease at diagnosis and will likely have a poor outcome. Other measures of poor outcome include poor performance status, presence of metastases, and an alkaline phosphatase level ≥100 U/L.⁴⁴ Additionally, nearly 80% of patients have involvement of the regional lymph nodes and the number of positive lymph nodes has a profound influence on survival.⁴⁵ In patients with localized resectable disease, outcome depends on the surgical stage of the disease.

Pathologic Review and Biomarker Testing

Pathologic review and biomarker testing play important roles in the diagnosis, classification, and molecular characterization of gastric cancer. Classification based on histologic subtype and molecular features helps improve

early diagnosis and has implications for therapy. An accumulation of genetic aberrations occurs during gastric carcinogenesis, including overexpression of growth factors and/or receptors, alterations in DNA damage response, and loss of genomic stability. Characterization of these pathways has enabled the application of molecular pathology to aid in the diagnosis, classification, and treatment of gastric cancer.¹⁵

Principles of Pathologic Review

A specific diagnosis of gastric adenocarcinoma should be established for staging and treatment purposes. Subclassification of gastric adenocarcinoma as intestinal or diffuse type may have implications for therapy since intestinal type tumors are more likely to be HER2 overexpression positive (see “Assessment of HER2 Overexpression,” page 174). In addition to the histologic type, the pathology report (regardless of the specimen type) should include specifics about tumor invasion and pathologic grade, which are required for staging (see GAST-B page 1 of 6, page 171). Universal testing for MSI by PCR/next-generation sequencing (NGS) or mismatch repair (MMR) deficiency by immunohistochemistry (IHC) is

PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Next-Generation Sequencing (NGS):

- At present, several targeted therapeutic agents, trastuzumab,^g pembrolizumab/nivolumab,ⁱ and entrectinib/larotrectinib have been approved by the FDA for use in gastric cancer. Trastuzumab is based on testing for HER2 overexpression. Pembrolizumab/nivolumab are based on testing for MSI by PCR or NGS/MMR by IHC, PD-L1 immunohistochemical expression, or high tumor mutational burden (TMB) by NGS. The FDA granted approval for the use of select TRK inhibitors for *NTRK* gene fusion-positive solid tumors. When limited tissue is available for testing, or the patient is unable to undergo a traditional biopsy, sequential testing of single biomarkers or use of limited molecular diagnostic panels may quickly exhaust the sample. In these scenarios, comprehensive genomic profiling via a validated NGS assay performed in a CLIA-approved laboratory may be used for the identification of HER2 amplification, MSI status, MMR deficiency, TMB, and *NTRK* gene fusions. The use of IHC/ISH/targeted PCR should be considered first followed by additional NGS testing as appropriate.

Liquid Biopsy^{7,8}

- The genomic alterations of solid cancers may be identified by evaluating circulating tumor DNA (ctDNA) in the blood, hence a form of “liquid biopsy.” Liquid biopsy is being used more frequently in patients with advanced disease, particularly those who are unable to have a clinical biopsy for disease surveillance and management. The detection of mutations/alterations in DNA shed from gastric carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. Therefore, for patients who have metastatic or advanced gastric cancer who may be unable to undergo a traditional biopsy, or for disease progression monitoring, testing using a validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered. A negative result should be interpreted with caution, as this does not exclude the presence of tumor mutations or amplifications.

^g An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

ⁱ See Guidelines for Management of Immunotherapy-Related Toxicities†.

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References*

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GAST-B
5 OF 6

recommended in all newly diagnosed patients. The pathology report of endoscopic mucosal resection specimens should include an assessment of lymphovascular invasion, depth of tumor invasion, tumor diameter and the status of mucosal and deep margins. Pathology reports of gastrectomy specimens without prior chemoradiation should also document the location of the tumor midpoint in relationship to the EGJ, whether the tumor crosses the EGJ, the lymph node status, and the number of lymph nodes recovered. In the case of gastrectomy with prior chemoradiation and without grossly obvious residual tumor, the tumor site should be thoroughly sampled to detect microscopic residual disease. The pathology report should include all of the above elements plus an assessment of treatment effect.

Principles of Biomarker Testing

Presently, IHC and/or molecular testing for HER2/*ERBB2* status, MSI or MMR status, PD-L1 expression, tumor mutation burden-high (TMB-H) status, and neurotrophic tropomyosin-related kinase (*NTRK*) gene fusions are implicated in the clinical management of advanced gastric cancer. When limited tissue is available for testing or the patient is unable to undergo a traditional biopsy,

comprehensive genomic profiling via a validated NGS assay performed in a CLIA-approved environment may be used for the identification of *ERBB2* amplification, MSI status, MMR deficiency, TMB and *NTRK* gene fusions. The use of IHC, in situ hybridization (ISH), or targeted PCR should be considered first, followed by NGS testing as appropriate.

Assessment of HER2 Overexpression

Overexpression of the HER2 protein or amplification of the *ERBB2* gene has been implicated in the development of gastric adenocarcinoma.⁴⁶ However, unlike in breast cancer, the prognostic significance of HER2 status in gastric cancer is unclear. Some studies suggest that HER2 positivity is associated with poor prognosis^{47–52} whereas others have shown that it is not an independent prognostic factor of patient outcome, except in a very small subgroup of patients with intestinal histology.^{53–55} Although further studies are needed to assess the prognostic significance of HER2 status in gastric cancer, the addition of HER2 monoclonal antibodies to chemotherapy regimens is a promising treatment option for patients with HER2 overexpression positive disease.

PRINCIPLES OF MULTIDISCIPLINARY TEAM APPROACH FOR ESOPHAGOGASTRIC CANCERS

Category 1 evidence supports the notion that the combined modality therapy is effective for patients with localized esophagogastric cancer.^{1,2,3} The NCCN Panel believes in an infrastructure that encourages multidisciplinary treatment decision-making by members of all disciplines taking care of this group of patients.

The combined modality therapy for patients with localized esophagogastric cancer may be optimally delivered when the following elements are in place:

- The involved institution and individuals from relevant disciplines are committed to jointly reviewing the detailed data on patients on a regular basis. Frequent meetings (either once a week or once every two weeks) are encouraged.
- Optimally at each meeting, all relevant disciplines should be encouraged to participate and these may include: surgical oncology, medical oncology, gastroenterology, radiation oncology, radiology, and pathology. In addition, the presence of nutritional services, social workers, nursing, palliative care specialists, and other supporting disciplines are also desirable.
- All long-term therapeutic strategies are best developed after adequate staging procedures are completed, but ideally prior to any therapy that is rendered.
- Joint review of the actual medical data is more effective than reading reports for making sound therapy decisions.
- A brief documentation of the consensus recommendation(s) by the multidisciplinary team for an individual patient may prove useful.
- The recommendations made by the multidisciplinary team may be considered advisory to the primary group of treating physicians of the particular patient.
- Re-presentation of select patient outcomes after therapy is rendered may be an effective educational method for the entire multidisciplinary team.
- A periodic formal review of relevant literature during the course of the multidisciplinary meeting is highly encouraged.

¹ Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20.

² Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 1999;281:1623-1627.

³ Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725-730.

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GAST-E

The reported rates of HER2 positivity in patients with gastric cancer range from 12% to 23%.^{48,49,54-57} HER2 positivity also varies with the histologic subtype (intestinal > diffuse) and tumor grade (moderately differentiated greater than poorly differentiated).^{49,54-56} HER2 positivity is reported in ≤20% of European and United States patients with metastatic gastric cancer with significantly higher rates seen in patients with intestinal histology (33% vs 8% for diffuse/mixed histology; $P=.001$).⁵⁴ In the US population, the reported HER2 positivity rate in gastric cancer is 12% and is more often identified in the intestinal subtype rather than the diffuse subtype (19% and 6%, respectively).⁵⁵ The HER-EAGLE study, which examined the HER2 positivity rate in a large multinational population of nearly 5,000 patients with gastric or EGJ adenocarcinoma, reported that 14.2% of samples were HER2 overexpression positive.⁵⁸ HER2 positivity was significantly higher in males versus females, in EGJ tumors versus stomach tumors, and in intestinal subtypes versus diffuse subtypes. In the ToGA trial that evaluated the addition of trastuzumab to chemotherapy in patients with HER2 overexpression positive advanced gastric or EGJ cancers, HER2 positivity rates were 32.2%, 21.4%, 31.8%, and 6.1%, respectively, in patients with EGJ

adenocarcinoma, gastric adenocarcinoma, intestinal gastric adenocarcinoma, and diffuse gastric adenocarcinoma.^{59,60} Therefore, subclassification of gastric adenocarcinomas as intestinal or diffuse type may have implications for therapy.

HER2 testing is recommended for all patients with gastric cancer at diagnosis if metastatic disease is documented or suspected (see GAST-1 and 1A, pages 168 and 169). In concordance with HER2 testing guidelines from the College of American Pathologists, the American Society for Clinical Pathology, and ASCO,⁶¹ the NCCN Guidelines recommend using IHC and, if needed, ISH techniques to assess HER2 status in gastric cancer (see GAST-B 3 of 6, page 172). NGS can be considered instead of sequential testing for single biomarkers when limited diagnostic tissue is available or when the patient is unable to undergo a traditional biopsy. The use of IHC/ISH should be considered first, followed by NGS testing as appropriate. Repeat biomarker testing may be considered at clinical or radiologic progression of advanced or metastatic disease.

IHC evaluates the membranous immunostaining of tumor cells, including the intensity and extent of staining and the percentage of immunoreactive tumor cells, with

PRINCIPLES OF SYSTEMIC THERAPY

- Systemic therapy regimens recommended for advanced esophageal and EGJ adenocarcinoma, squamous cell carcinoma of the esophagus, and gastric adenocarcinoma may be used interchangeably (except as indicated).
- Regimens should be chosen in the context of performance status (PS), medical comorbidities, and toxicity profile.
- Trastuzumab^a should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma.
- Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. The use of three cytotoxic drugs in a regimen should be reserved for medically fit patients with excellent PS and easy access to frequent toxicity evaluations.
- Modifications of category 1 regimen or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting a more favorable toxicity profile without compromising efficacy.¹
- Doses and schedules for any regimen that is not derived from category 1 evidence are a suggestion, and are subject to appropriate modifications depending on the circumstances.
- Alternate combinations and schedules of cytotoxics based on the availability of the agents, practice preferences, and contraindications are permitted.
- Perioperative therapy^{2,3} is a category 1 recommendation for localized gastric cancer. Postoperative chemotherapy plus chemoradiation⁴ is an alternative option for patients who received less than a D2 lymph node dissection.
- Postoperative chemotherapy is recommended following primary D2 lymph node dissection.^{5,6} (See Principles of Surgery [GAST-C*])
- In the adjuvant setting, upon completion of chemotherapy or chemoradiation, patients should be monitored for any long-term therapy-related complications.

Footnotes

^a An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

References

- 1 Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006;24:4991-4997.
- 2 Ychou M, Boige V, Pignon J-P, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011;29:1715-1721.
- 3 Al-Batran S-E, 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;393:1948-1957.

- 4 Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol* 2012;30:2327-2333. (See GAST-F 7 of 16).
- 5 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; 15:1389-1396.
- 6 Park SH, Sohn TS, Lee J, et al. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. *J Clin Oncol* 2015;33:3130-3136.

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GAST-F
1 OF 16

scores ranging from 0 (negative) to 3+ (positive). In 2008, Hofmann et al⁶² refined this 4-tiered scoring system to assess HER2 status in gastric cancer by using a cut-off of $\geq 10\%$ immunoreactive tumor cells.⁶⁰ In a subsequent validation study (n=447 prospective diagnostic gastric cancer specimens), this scoring system was found to be reproducible between different pathologists.⁶³ This modified HER2 scoring system is therefore recommended by the panel. A score of 0 (membranous reactivity in $< 10\%$ of cancer cells) or 1+ (faint membranous reactivity in $\geq 10\%$ of cancer cells) is considered to be HER2-negative. A score of 2+ (weak to moderate membranous reactivity in $\geq 10\%$ of cancer cells) is considered equivocal and should be additionally examined by fluorescence in situ hybridization (FISH) or other ISH methods. FISH/ISH results are expressed as the ratio between the number of copies of the *ERBB2* gene and the number of chromosome 17 centromeres (CEP17) within the nucleus counted in at least 20 cancer cells (*ERBB2*:CEP17). Alternatively, FISH/ISH results may be given as the average *ERBB2* copy number per cell. Cases that have an IHC score of 3+ (strong membranous reactivity in $\geq 10\%$ of cancer cells) or an IHC score of 2+ and are FISH/ISH positive (*ERBB2*:CEP17 ratio ≥ 2 or average *ERBB2* copy

number ≥ 6 signals/cell) are considered HER2 overexpression positive. Positive (3+) or negative (0 or 1+) HER2 IHC results do not require further ISH testing.

MSI or MMR Testing

Universal testing for MSI by PCR/NGS or MMR by IHC should be performed for all newly diagnosed gastric cancer patients (see GAST-1/1A). MSI status is assessed by PCR to measure gene expression levels of microsatellite markers (ie, *BAT25*, *BAT26*, *MONO27*, *NR21*, *NR24*).⁶⁴ MMR deficiency is evaluated by IHC to assess nuclear expression of proteins involved in DNA mismatch repair (ie, MLH1, MSH2, MSH6, PMS2).⁶⁵ PCR/NGS for MSI and IHC for MMR proteins measure different biologic effects caused by deficient MMR function. Testing is performed on formalin-fixed, paraffin-embedded tissue and results are interpreted as MSI-high (MSI-H) or MMR-deficient (dMMR) in accordance with College of American Pathologists DNA Mismatch Repair Biomarker Reporting Guidelines (see GAST-B 4 of 6, page 173).⁶⁶ Patients with MSI-H or dMMR tumors should be referred to a genetics counselor for further assessment in the appropriate clinical context.

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy • Oxaliplatin is generally preferred over cisplatin due to lower toxicity.
Preferred Regimens • HER2 overexpression positive adenocarcinoma ^f Fluoropyrimidine (fluorouracil ^b or capecitabine) and oxaliplatin and trastuzumab ^a Fluoropyrimidine (fluorouracil ^b or capecitabine) and cisplatin and trastuzumab (category 1) ^{a,11} • HER2 overexpression negative ^f Fluoropyrimidine (fluorouracil ^b or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) (category 1) ^{g,h,12} Fluoropyrimidine (fluorouracil ^b or capecitabine) and oxaliplatin ¹³⁻¹⁵ Fluoropyrimidine (fluorouracil ^b or capecitabine) and cisplatin ^{13,16-18}
Other Recommended Regimens • HER2 overexpression positive adenocarcinoma ^f Fluoropyrimidine (fluorouracil ^b or capecitabine) and cisplatin and trastuzumab ^a and pembrolizumab ^{g,h,19} Fluoropyrimidine (fluorouracil ^b or capecitabine) and oxaliplatin and trastuzumab ^a and pembrolizumab ^{g,h,19} • Fluorouracil ^{b,i} and irinotecan ^{j,20} • Paclitaxel with or without cisplatin or carboplatin ^{j,21-25} • Docetaxel with or without cisplatin ^{j,26-29} • Fluoropyrimidine ^{j,17,30,31} (fluorouracil ^b or capecitabine) • Docetaxel, cisplatin or oxaliplatin, and fluorouracil ^{b,j,32,33} • Docetaxel, carboplatin, and fluorouracil (category 2B) ^{j,34}
Useful in Certain Circumstances • HER2 overexpression negative ^f Fluoropyrimidine (fluorouracil ^b or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS <5) (category 2B) ^{g,h,12}

^a An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

^b Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.

^f See Principles of Pathologic Review and Biomarker Testing (GAST-B⁴).

^g If no prior tumor progression while on therapy with a checkpoint inhibitor.

^h See NCCN Guidelines for Management of Immunotherapy-Related Toxicities[†].

ⁱ Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.

^j Trastuzumab should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma. An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

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GAST-F
3 OF 16

PD-L1 Testing

PD-L1 testing may be considered on locally advanced, recurrent, or metastatic gastric cancers in patients who are candidates for treatment with PD-1 inhibitors (see GAST-B 4 of 6, page 173). A US FDA approved companion diagnostic test should be used to identify patients for treatment with PD-1 inhibitors. The companion diagnostic test is a qualitative IHC assay using anti-PD-L1 antibodies for the detection of PD-L1 protein levels in formalin-fixed, paraffin-embedded tumor tissue. A minimum of 100 tumor cells must be present in the PD-L1-stained slide for the specimen to be adequately evaluated. Combined positive score (CPS) is determined by the number of PD-L1-stained cells (ie, tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells evaluated, multiplied by 100. A specimen is considered to have PD-L1 expression if the CPS ≥1. Tumor proportion score is also considered and reported in some trials.

Liquid Biopsy

The genomic alterations of solid cancers may be identified by evaluating circulating tumor DNA (ctDNA) in the blood, hence a form of “liquid biopsy.”^{51,67} Liquid biopsy

is being used more frequently in patients with advanced disease, particularly those who are unable to have a clinical biopsy for disease surveillance and management. The detection of mutations/alterations in DNA shed from gastric carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. In one study, a complete or partial response to immunotherapy was achieved by 63% of patients with advanced gastric carcinoma who tested positive for MSI by cell-free DNA analysis.⁶⁷ In another study that analyzed the genomic alterations of 55 patients with advanced gastroesophageal adenocarcinomas using NGS performed on plasma-derived ctDNA, 69% of patients had ≥1 characterized alteration theoretically targetable by an FDA-approved agent (on- or off-label).⁵¹ Therefore, for patients who have advanced or metastatic gastric cancer and who may be unable to undergo a traditional biopsy or for disease progression monitoring, testing using a validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered (see GAST-B 5 of 6, page 174). A negative result should be interpreted with caution, as this does not exclude the presence of tumor mutations or amplifications.

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy • Dependent on prior therapy and PS
Preferred Regimens • Ramucirumab and paclitaxel (category 1) ³⁵ • Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma ³⁶ • Docetaxel (category 1) ^{28,29} • Paclitaxel (category 1) ^{24,25,37} • Irinotecan (category 1) ³⁷⁻⁴⁰ • Fluorouracil ^{b,i} and irinotecan ^{38,41,42} • Trifluridine and tipiracil for third-line or subsequent therapy (category 1) ⁴³
Other Recommended Regimens • Ramucirumab (category 1) ⁴⁴ • Irinotecan and cisplatin ^{14,45} • Fluorouracil and irinotecan + ramucirumab ^{b,i,46} • Irinotecan and ramucirumab ⁴⁷ • Docetaxel and irinotecan (category 2B) ⁴⁸
Useful in Certain Circumstances • Entrectinib or larotrectinib for <i>NTRK</i> gene fusion-positive tumors ^{49,50} • Pembrolizumab ^{9,h} for MSI-H or dMMR tumors ⁵¹⁻⁵³ • Pembrolizumab ^{9,h} for TMB high (≥10 mutations/megabase) tumors ⁵⁴ • Dostarlimab-gxly ^{9,h,k} for MSI-H or dMMR tumors ⁵⁵

^b Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.

^g If no prior tumor progression while on therapy with a checkpoint inhibitor.

^h See NCCN Guidelines for Management of Immunotherapy-Related Toxicities[†].

ⁱ Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.

^k For patients whose cancer is progressing on or following prior treatment (that did not include a checkpoint inhibitor like PD-1i, PDL-1i, or CTLA4i) and who have no satisfactory alternative treatment options. Prior use of immuno-oncology therapy in these patients will make them ineligible for dostarlimab-gxly.

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References***

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**GAST-F
4 OF 16**

Treatment Guidelines

The management of patients with gastric cancer requires the expertise of several disciplines, including surgical oncology, medical oncology, radiation oncology, gastroenterology, radiology, and pathology. In addition, the presence of nutritional services, social workers, nurses, palliative care specialists, and other supporting disciplines is also desirable.⁶⁸ Hence, the panel believes in an infrastructure that encourages multidisciplinary treatment decision-making by members of all disciplines taking care of patients with gastric cancer (see GAST-E, page 175). The recommendations made by the multidisciplinary team may be considered advisory to the primary group of treating physicians.

Workup

Newly diagnosed patients should receive a complete history and physical examination, complete blood count (CBC), comprehensive chemistry profile, and upper gastrointestinal endoscopy with biopsy of the primary tumor (see GAST-1 and GAST-1A, pages 168 and 169). CT scan (with oral and intravenous contrast) of the chest, abdomen, and pelvis should also be performed. FDG-PET/CT

evaluation from skull base to midhigh is recommended, if clinically indicated and if metastatic disease is not evident (may not be appropriate for T1 disease). EUS should be performed if early-stage disease is suspected or if early-stage versus locally advanced disease needs to be determined (preferred). Endoscopic resection is essential for the accurate staging of early-stage cancers (T1a or T1b); early-stage cancers can best be diagnosed by endoscopic resection. Endoscopic resection may also be therapeutic for early-stage disease. Biopsy of metastatic disease should be performed as clinically indicated. Assessment of Siewert tumor type should also be included as part of the initial workup in all patients with EGJ adenocarcinoma.^{69,70} Nutritional assessment and counseling as well as smoking cessation advice, counseling, and pharmacotherapy (as indicated) are recommended for all patients.

Universal testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients. HER2 and PD-L1 testing are recommended at the time of diagnosis if metastatic disease is documented or suspected. NGS may be considered via a validated assay. The guidelines also recommend screening for family

PRINCIPLES OF PALLIATIVE CARE/BEST SUPPORTIVE CARE^a

The goal of best supportive care is to prevent and relieve suffering and to support the best possible quality of life for patients and their families, regardless of the stage of the disease or the need for other therapies. For gastric cancer, interventions undertaken to relieve major symptoms may result in prolongation of life. This appears to be particularly true when a multimodality interdisciplinary approach is pursued, and, therefore, a multimodality interdisciplinary approach to palliative care of the gastric cancer patient is encouraged.^b

Bleeding

- Acute bleeding is common in patients with gastric cancer and may directly arise from the tumor or as a consequence of therapy. Patients with acute severe bleeding (hematemesis or melena) should undergo prompt endoscopic assessment.¹

Endoscopic Treatment

- ◊ The efficacy of endoscopic therapy for bleeding in patients with gastric cancer is not well studied.² The limited data suggest that while endoscopic therapies may initially be effective, the rate of recurrent bleeding is very high.³
- ◊ Widely available treatment options include injection therapy, mechanical therapy (eg, endoscopic clips), ablative therapy (eg, argon plasma coagulation), or a combination of methods.

Interventional Radiology

- ◊ Angiographic embolization techniques may be useful in those situations where endoscopy is not helpful or bleeding occurs.

External beam radiation therapy (EBRT) has been shown to effectively manage acute and chronic gastrointestinal bleeding in multiple small series.^{4,5}

- Chronic blood loss from gastric cancer

Although proton pump inhibitors can be prescribed to reduce bleeding risk from gastric cancer, there are no definite data supporting its use at this time.

EBRT may be used for chronic blood loss due to gastric cancer.^{4,5}

^a See NCCN Guidelines for Palliative Care[†].

^b For patients who have immune-mediated toxicity, See NCCN Guidelines for Management of Immunotherapy-Related Toxicities[†].

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GAST-J
1 OF 3

history of gastric cancers. Referral to a cancer genetics professional is recommended for those with a family history or a known high-risk syndrome associated with gastric cancer.

Initial workup enables patients to be classified into 3 clinical stage groups:

- Localized cancer (stages cTis or cT1a)
- Locoregional cancer (stages cT1b–cT4a; cM0)
- Metastatic cancer (stage cT4b; cM1)

Unresectable Locally Advanced, Recurrent, or Metastatic Disease

Management of unresectable or metastatic disease may include either systemic therapy and/or chemoradiation with the goal of providing symptom relief and delaying progression, and should incorporate symptom-directed best supportive care (See “Palliative/Best Supportive Care,” page 186). If not done previously, HER2, PD-L1, and MSI or MMR testing should be performed in patients with documented or suspected metastatic adenocarcinoma. NGS may be considered via a validated assay (see GAST-9, page 170).

The decision to offer palliative/best supportive care alone or with systemic therapy is dependent on the patient's performance status. The ECOG Performance Status (PS) Scale and the Karnofsky PS Scale (KPS) are commonly used to assess the performance status of patients with cancer.^{71–73} Patients with higher ECOG PS scores are considered to have worse performance status while lower KPS scores are associated with worse survival for most serious illnesses. Patients with a KPS score <60% or an ECOG PS score ≥3 should be offered palliative/best supportive care only. Systemic therapy or chemoradiation (only if locally unresectable and not previously received) can be offered in addition to palliative/best supportive care for patients with better performance status (KPS score of ≥60% or ECOG PS score ≤2).

The survival benefit of systemic therapy compared with palliative/best supportive care alone for patients with advanced gastric cancer has been shown in several randomized trials.^{74–77} In an early comparison between chemotherapy and best supportive care versus best supportive care alone, overall survival (OS; 8 vs 5 months) and time to progression (5 vs 2 months) were longer in patients receiving chemotherapy in addition to best supportive care for advanced gastric cancer.⁷⁴ More patients

PRINCIPLES OF PALLIATIVE CARE/BEST SUPPORTIVE CARE^a**Obstruction**

The primary goals of palliation for patients with malignant gastric obstruction are to reduce nausea and vomiting and, when possible, allow resumption of an oral diet.

- Alleviate or bypass obstruction

- Endoscopy

- ◊ Placement of enteral stent for relief of outlet obstruction,⁶ or esophageal stent for EGJ/gastric cardia obstruction (see NCCN Guidelines for Esophageal and Esophagogastric Junction Cancers¹)

- Surgery

- ◊ Gastrojejunostomy⁶
 - ◊ Gastrectomy in select patients⁷

- EBRT

- Chemotherapy^b

- When obstruction cannot be alleviated or bypassed, the primary goal is to reduce the symptoms of obstruction via venting gastrostomy (if endoscopic lumen enhancement is not undertaken or is unsuccessful).⁸

Percutaneous, endoscopic, surgical, or interventional radiology gastrostomy tube placement can be placed for gastric decompression if tumor location permits.

Ascites, if present, should be drained prior to venting gastrostomy tube placement to reduce the risk of infectious complications.

- In patients who cannot take an oral diet, feeding gastrostomy tubes for patients with EGJ/gastric cardia obstruction or jejunal feeding tubes for patients with mid and distal gastric obstruction can be placed if tumor location permits.

Pain

- EBRT

- Chemotherapy^c

- If patient is experiencing tumor-related pain, then the pain should be assessed and treated in accordance with the NCCN Guidelines for Adult Cancer Pain[†].

Nausea/Vomiting

- If patient is experiencing nausea and vomiting, then the patient should be treated in accordance with the NCCN Guidelines for Antiemesis[†].
- Nausea and vomiting may be associated with luminal obstruction, so endoscopic or fluoroscopic evaluation should be performed to determine if obstruction is present.

^a See NCCN Guidelines for Palliative Care[†].

^c See Principles of Systemic Therapy (GAST-F).

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GAST-J
2 OF 3

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in the chemotherapy group (45%) had an improved or prolonged quality of life for a minimum of 4 months compared with those who received best supportive care alone (20%). In a more recent randomized phase III study, the addition of second-line chemotherapy with irinotecan significantly prolonged OS compared with best supportive care alone in patients with metastatic or locally advanced gastric or EGJ adenocarcinoma (n=40).⁷⁵ Median survival was 4 months in the irinotecan and best supportive care group compared with 2.4 months in the best supportive care alone group. However, the study was closed prematurely due to poor accrual. In a larger randomized trial (n=193), second-line chemotherapy with irinotecan (or docetaxel) was also found to significantly improve OS compared with best supportive care alone (5.1 vs 3.8 months) in patients with advanced gastric cancer.⁷⁶ In another phase III randomized trial, the addition of docetaxel to best supportive care was associated with a survival benefit for patients with advanced adenocarcinoma of the esophagus (n=33), EGJ (n=59), or stomach (n=76) that had progressed on or within 6 months of treatment with platinum and fluoropyrimidine-based combination chemotherapy.⁷⁷ After a median follow-up of 12 months, the median OS was 5.2

months for patients in the docetaxel and best supportive care group compared with 3.6 months for those in the best supportive care alone group ($P=.01$). Therefore, the addition of systemic therapy to best supportive care may prolong survival in patients with advanced gastric cancer.

Systemic Therapy for Locally Advanced or Metastatic Disease

First-Line Therapy

Systemic therapy can provide palliation of symptoms, improved survival, and enhanced quality of life in patients with locally advanced or metastatic gastric cancer.^{74–77} First-line systemic therapy regimens with 2 cytotoxic drugs are preferred for patients with advanced disease because of their lower toxicity. The use of 3 cytotoxic drugs in a regimen should be reserved for medically fit patients with excellent PS and easy access to frequent toxicity evaluations (see GAST-F 1 of 16, page 176).⁷⁸ Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

Trastuzumab should be added to first-line chemotherapy for patients with HER2 overexpression positive

adenocarcinoma (combination with a fluoropyrimidine and a platinum agent is preferred [category 1 for cisplatin⁶⁰; category 2A for oxaliplatin]; see GAST-F 3 of 16, page 177). An FDA-approved biologic medical product that is similar to trastuzumab (a biosimilar) is an appropriate substitute. Pembrolizumab can also be added to this regimen for treatment of HER2 overexpression positive adenocarcinoma.⁷⁹ Preferred regimens for HER2 overexpression negative disease include nivolumab combined with fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin for tumors with PD-L1 expression levels by CPS of ≥ 5 (category 1).⁸⁰ Nivolumab is useful under certain circumstances for tumors with CPS of < 5 (category 2B). See “Targeted Therapies” (next column) for more information on trastuzumab, nivolumab, and pembrolizumab.

The preferred regimens for HER2 negative disease also include a fluoropyrimidine (fluorouracil or capecitabine) combined with either oxaliplatin^{81–83} or cisplatin.^{81,84–86} A phase III trial conducted by the German Study Group compared treatment with fluorouracil and cisplatin to FOLFOX in patients (n=220) with previously untreated advanced adenocarcinoma of the stomach or EGJ.⁸¹ Results showed that FOLFOX (referred to as *FLO*) was associated with significantly less toxicity and showed a trend toward improved median progression-free survival (PFS; 5.8 vs 3.9 months; $P=.77$) compared with fluorouracil and cisplatin (FLP).⁸¹ However, no significant difference in median OS (10.7 vs 8.8 months, respectively) was seen between the 2 groups. FOLFOX resulted in significantly superior response rates (41.3% vs 16.7%; $P=.12$), time to treatment failure (5.4 vs 2.3 months; $P<.001$), PFS (6.0 vs 3.1 months; $P=.029$), and improved OS (13.9 vs 7.2 months) compared with FLP in patients > 65 years (n=94). Therefore, FOLFOX offers reduced toxicity and similar efficacy compared with fluorouracil plus cisplatin and may also be associated with improved efficacy in older adult patients. The safety and efficacy of FOLFOX has also been demonstrated in other studies.^{82,87,88}

Regimens combining a platinum agent with capecitabine have also been evaluated in several studies for patients with advanced gastric cancer.^{86,89,90} A phase III randomized trial (ML 17032) that evaluated the efficacy of combined capecitabine and cisplatin (XP) compared with fluorouracil and cisplatin (FP) found that capecitabine was noninferior to fluorouracil as first-line therapy in patients with advanced gastric cancer.⁸⁶ Two phase II trials concluded that capecitabine in combination with oxaliplatin is active and well-tolerated as first-line therapy for advanced gastric cancer.^{89,90} Furthermore, results of a meta-analysis suggest that OS was superior in advanced gastroesophageal cancer patients treated with capecitabine-based combinations compared with patients

treated with fluorouracil-based combinations, although no significant difference in PFS between treatment groups was seen.⁹¹ Another meta-analysis reported that treatment with oxaliplatin-based regimens significantly improved the partial response rate, disease progression rate, and 1-year OS rate of patients with gastric cancer as compared with cisplatin-based regimens.⁹² Therefore, capecitabine and oxaliplatin is also a preferred regimen for first-line treatment of patients with advanced gastric cancers. The GO2 phase III trial demonstrated that a low-dose capecitabine and oxaliplatin regimen (60% of the standard dose) was noninferior in terms of PFS and resulted in significantly lower toxicities and better overall treatment utility in elderly and/or frail patients with advanced gastroesophageal cancers (n=514).⁹³ Therefore, this low-dose regimen is recommended as an alternative to standard-dose capecitabine and oxaliplatin for elderly and/or frail patients with advanced or metastatic disease.

First-line treatment with irinotecan-based regimens has been explored extensively in clinical trials involving patients with advanced or metastatic gastroesophageal cancers.^{85,94–105} The results of a randomized phase III study comparing irinotecan and fluorouracil (FOLFIRI) to cisplatin and fluorouracil (CF) in patients with advanced gastric or EGJ adenocarcinoma (n=337) showed that FOLFIRI was noninferior to CF in terms of PFS, but not in terms of OS or time to progression.¹⁰⁰ FOLFIRI was also associated with a more favorable safety profile. A phase III trial (French Intergroup Study) compared FOLFIRI with epirubicin, cisplatin, and fluorouracil (ECF) as first-line treatment in patients (n=416) with advanced or metastatic gastric or EGJ adenocarcinoma.¹⁰⁵ After a median follow-up of 31 months, median time to treatment failure was significantly longer with FOLFIRI than with ECF (5.1 vs 4.2 months; $P=.008$).¹⁰⁵ However, there were no significant differences in median PFS (5.3 vs 5.8 months; $P=.96$), median OS (9.5 vs 9.7 months; $P=.95$), or response rate (39.2% vs 37.8%). Importantly, FOLFIRI was less toxic and better tolerated than ECF. Therefore, FOLFIRI may be recommended as an option for first-line therapy in patients with advanced or metastatic gastric cancer.

Docetaxel, cisplatin, and fluorouracil (DCF) has also demonstrated activity in patients with locally advanced or metastatic gastric cancer.^{106,107} An international phase III study (V325) that randomized 445 patients with untreated advanced gastric or EGJ cancer to receive either DCF or cisplatin and fluorouracil (CF) found that the addition of docetaxel to CF significantly improved time to progression, OS, and overall response rate (ORR).¹⁰⁶ However, DCF was associated with increased toxicities including myelosuppression and infectious complications. Various modifications of the DCF regimen have demonstrated improved safety in clinical trials of

patients with advanced gastric cancer compared with the DCF regimen evaluated in the V325 study.^{108–113} Therefore, due to concerns regarding toxicity, dose-modified DCF or other DCF modifications should be used as alternative options to the standard DCF regimen for first-line therapy.^{109,112,113} Other recommended regimens for first-line therapy include paclitaxel with either cisplatin or carboplatin,^{114–116} docetaxel with cisplatin,^{117,118} or single-agent fluoropyrimidine (fluorouracil or capecitabine),^{85,119,120} docetaxel,^{77,121} or paclitaxel.^{122,123} Docetaxel, carboplatin, and fluorouracil¹⁰⁹ is a category 2B recommendation in this setting.

Second-Line and Subsequent Therapy

The selection of regimens for second-line or subsequent therapy is dependent on prior therapy and performance status (see GAST-F 4 of 16, page 178). Ramucirumab in combination with paclitaxel (preferred) or as a single agent are category 1 recommendations for second-line or subsequent therapy.^{124,125} Fam-trastuzumab deruxtecan-nxki is a second-line treatment option for patients with HER2 overexpression-positive adenocarcinoma who had received prior trastuzumab-based therapy.¹²⁶ See “Targeted Therapies,” (next column) for more information on ramucirumab and fam-trastuzumab deruxtecan-nxki.

Single-agent docetaxel,^{77,121} paclitaxel,^{122,123,127} and irinotecan^{75,127–129} are also category 1 preferred options for second-line or subsequent therapy. In a randomized phase III trial (COUGAR-02) single-agent docetaxel was shown to significantly increase 12-month OS compared with active symptom control alone (5.2 vs 3.6 months, respectively; hazard ratio [HR] =0.67; $P=.01$).⁷⁷ A randomized phase III trial comparing second-line therapy with paclitaxel to irinotecan in patients with advanced gastric cancer found similar OS between the 2 groups (9.5 months in the paclitaxel group vs 8.4 months in the irinotecan group; HR=1.13; $P=.38$).¹²⁷

FOLFIRI is a preferred treatment option that can be safely used in the second-line setting if it was not previously used in first-line therapy.^{96,129–132} A phase II trial investigating the efficacy and toxicity of FOLFIRI in patients (n=40) with recurrent or metastatic gastric cancer reported an ORR of 29% and median OS of 6.4 months.¹³² Another phase II trial reported similar results with an ORR of 20% and OS of 6.7 months in advanced gastric cancer patients (n=59) treated with FOLFIRI in the second-line setting.¹²⁹ Additionally, FOLFIRI was shown to be an effective and safe treatment option in a cohort of patients with metastatic gastric or EGJ cancers refractory to docetaxel-based chemotherapy.¹³⁰ In this study, the ORR was 22.8% and median PFS and OS were 3.8 and 6.2 months, respectively. The most common grade 3–4 toxicities were neutropenia (28.5%) and diarrhea (14.5%).

The trifluridine and tipiracil regimen was approved by the FDA in 2019 for previously treated recurrent or metastatic gastric and EGJ adenocarcinoma,¹³³ based on results from the global phase III TAGS trial, in which 507 patients with heavily pretreated metastatic gastric or EGJ cancer were randomized 2:1 to receive trifluridine and tipiracil plus best supportive care (n=337) or placebo plus best supportive care (n=170).¹³⁴ This study reported an improvement in median OS by 2.1 months (5.7 vs 3.6 months) with the trifluridine and tipiracil regimen compared with placebo (HR=0.69; 95% CI, 0.56–0.85; $P=.0003$). PFS was significantly longer in the trifluridine and tipiracil group (2.0 vs 1.7 months; HR=0.57; 95% CI, 0.47–0.70; $P<.0001$). The efficacy benefits of trifluridine and tipiracil were observed regardless of whether the patient had undergone previous gastrectomy.¹³⁵ The most frequently reported grade 3–4 toxicities were neutropenia (38%), leukopenia (21%), anemia (19%), and lymphocytopenia (19%). Patients aged ≥ 65 years had a higher incidence of moderate renal impairment compared with the overall study population (31% vs 17%).¹³⁶ Trifluridine and tipiracil is recommended as a preferred category 1 treatment option for patients with recurrent or metastatic gastric cancer in the third-line or subsequent setting. However, trifluridine and tipiracil did not result in any partial or complete responses and produced substantial grade 3–4 toxicities. Therefore, this treatment should be considered for a very select population of patients with low-volume gastric cancer who have minimal or no symptoms and the ability to swallow pills.

Other recommended regimens for second-line or subsequent therapy include irinotecan and cisplatin,^{82,137} ramucirumab combined with irinotecan¹³⁸ or FOLFIRI,¹³⁹ and irinotecan and docetaxel (category 2B).¹⁴⁰ Options that are useful in certain circumstances include pembrolizumab^{65,141,142} or dostarlimab-gxly¹⁴³ for MSI-H/dMMR tumors, pembrolizumab for TMB-H (≥ 10 mutations/megabase) tumors,¹⁴⁴ and entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors.^{145,146} See “Targeted Therapies” (below) for more information on pembrolizumab, dostarlimab-gxly, entrectinib, and larotrectinib.

Targeted Therapies

At present, several targeted therapeutic agents, trastuzumab, pembrolizumab/nivolumab, and entrectinib/larotrectinib, have been approved by the FDA for use in advanced gastric cancer. Treatment with trastuzumab is based on the presence of HER2 overexpression.⁶⁰ Treatment with pembrolizumab/nivolumab is based on testing for MSI by PCR/NGS or MMR by IHC, PD-L1 expression by IHC, or high TMB by NGS.^{65,80,141,142,144,147,148} Treatment with the TRK inhibitors entrectinib and larotrectinib is based on testing for *NTRK* gene fusions.^{149,150} The use of IHC/ISH/targeted PCR should be considered first, followed

by NGS testing as appropriate for the identification of *ERBB2* amplification, MSI status, MMR deficiency, TMB, and *NTRK* gene fusions.

Trastuzumab

The ToGA trial was the first randomized prospective phase III trial that evaluated the efficacy and safety of trastuzumab in patients with HER2 overexpression positive advanced gastric or EGJ adenocarcinoma.⁶⁰ In this trial, 594 patients with HER2 overexpression-positive, locally advanced, recurrent, or metastatic gastric or EGJ adenocarcinoma were randomized to receive trastuzumab plus chemotherapy (cisplatin plus fluorouracil or capecitabine) or chemotherapy alone.⁶⁰ The majority of patients had gastric cancer (80% in the trastuzumab group and 83% in the chemotherapy group). Median follow-up was 19 and 17 months, respectively, in the 2 groups. Results showed significant improvement in median OS with the addition of trastuzumab to chemotherapy in patients with HER2 overexpression-positive disease (13.8 vs 11 months, respectively; $P=.046$). This study established trastuzumab in combination with cisplatin and a fluoropyrimidine as the standard treatment for patients with HER2 overexpression-positive advanced gastroesophageal adenocarcinoma. In a posthoc subgroup analysis, the addition of trastuzumab to chemotherapy further improved OS in patients whose tumors were IHC 2+ and FISH positive or IHC 3+ ($n=446$; 16 vs 11.8 months; HR=0.65) compared with those with tumors that were IHC 0 or 1+ and FISH positive ($n=131$; 10 vs 8.7 months; HR=1.07).

The phase II HERXO trial assessed the combination of trastuzumab with capecitabine and oxaliplatin in the first-line treatment of patients with HER2 overexpression positive advanced gastric or EGJ adenocarcinoma ($n=45$).¹⁵¹ At a median follow-up of 13.7 months, PFS and OS were 7.1 and 13.8 months, respectively, and 8.9%, 37.8%, and 31.1% of patients experienced a complete response, partial response, and stable disease. The most frequently reported grade 3 or higher adverse events were diarrhea (26.6%), fatigue (15.5%), nausea (20%), and vomiting (13.3%). In a retrospective study of 34 patients with HER2 overexpression-positive metastatic gastric or EGJ adenocarcinoma, the combination of trastuzumab with a modified FOLFOX regimen (mFOLFOX6) improved tolerability compared with the cisplatin plus fluorouracil regimen in previously untreated patients with HER2 overexpression-positive tumors.¹⁵² The ORR with this regimen was 41% and median PFS and OS were 9.0 and 17.3 months, respectively. The most frequent grade 3–4 toxicities were neutropenia (8.8%) and neuropathy (17.6%). These results suggest that the combinations of trastuzumab with capecitabine and oxaliplatin or with modified FOLFOX are effective regimens with acceptable safety

profiles in patients with HER2 overexpression positive gastroesophageal cancers. Therefore, trastuzumab should be added to first-line chemotherapy in combination with a fluoropyrimidine and a platinum agent (oxaliplatin is preferred over cisplatin due to lower toxicity) in patients with HER2 overexpression-positive adenocarcinoma. An FDA-approved biosimilar is an appropriate substitute for trastuzumab. Trastuzumab may be combined with other chemotherapy agents for first-line therapy, but should not be continued in second-line therapy.¹⁵³

Pembrolizumab can also be added to first-line fluoropyrimidine, platinum and trastuzumab based on an interim analysis of the first 264 patients enrolled in the KEYNOTE-811 trial, which showed an improved ORR (74% vs 52%; $P=.0001$) and median duration of response (10.6 vs 9.5 months) with the addition of pembrolizumab to chemotherapy plus trastuzumab compared with the addition of placebo in patients with HER2 overexpression positive adenocarcinoma.⁷⁹

Fam-Trastuzumab Deruxtecan-nxki

Fam-trastuzumab deruxtecan-nxki is an antibody-drug conjugate consisting of trastuzumab and a cytotoxic topoisomerase I inhibitor connected by a cleavable tetrapeptide-based linker. The efficacy and safety of fam-trastuzumab deruxtecan-nxki in advanced or metastatic gastric or EGJ adenocarcinoma was evaluated in the phase II DESTINY-Gastric01 trial, which included 188 patients with progressive disease after at least 2 prior lines of therapy, including trastuzumab.¹²⁶ Patients were randomized 2:1 to receive either fam-trastuzumab deruxtecan-nxki or physician's choice of chemotherapy (paclitaxel or irinotecan). The confirmed objective response rate for patients on fam-trastuzumab deruxtecan-nxki was 40.5% compared with 11% for those on chemotherapy. OS (12.5 vs 8.4 months; $P=.0097$), median PFS (5.6 vs 3.5 months), and median duration of response (11.3 vs 3.9 months) were also higher in the fam-trastuzumab deruxtecan-nxki group compared with the chemotherapy group. Fam-trastuzumab deruxtecan-nxki resulted in more toxicities than systemic chemotherapy in this trial. The most common adverse events (grade 3 or higher) were a decreased neutrophil count (51% of the fam-trastuzumab deruxtecan-nxki group and 24% of the chemotherapy group), anemia (38% and 23%, respectively), and decreased white-cell count (21% and 11%). Fam-trastuzumab deruxtecan-nxki-related interstitial lung disease or pneumonitis occurred in 12 patients resulting in 1 drug-related death (due to pneumonia). No drug-related deaths occurred in the physician's choice group. The FDA has approved fam-trastuzumab deruxtecan-nxki to treat patients with HER2 overexpression-positive tumor in the second or later line. Therefore, fam-trastuzumab deruxtecan-nxki may be used as a second-line or

subsequent treatment option for patients with HER2 overexpression–positive adenocarcinoma after failure of prior treatment with a trastuzumab-based regimen. However, careful patient selection and close monitoring of patients for excessive toxicity is recommended.

Ramucirumab

Ramucirumab, a VEGFR-2 antibody, has shown favorable results in patients with previously treated advanced or metastatic gastroesophageal cancers in two phase III clinical trials.^{124,125} An international randomized multicenter phase III trial (REGARD) demonstrated a survival benefit for ramucirumab in patients with advanced gastric or EGJ adenocarcinoma progressing after first-line chemotherapy.¹²⁴ In this study, 355 patients were randomized to receive ramucirumab (n=238) or placebo (n=117). Median OS was 5.2 months in patients treated with ramucirumab compared with 3.8 months for those in the placebo group ($P=.047$). Ramucirumab was associated with higher rates of hypertension than placebo (16% vs 8%), whereas rates of other adverse events were similar.

An international phase III randomized trial (RAINBOW) evaluated paclitaxel with or without ramucirumab in patients (n=665) with metastatic gastric or EGJ adenocarcinoma progressing on first-line chemotherapy.¹²⁵ Patients randomized to receive ramucirumab plus paclitaxel (n=330) had significantly longer median OS (9.63 months) compared with patients receiving paclitaxel alone (n=335; 7.36 months; $P<.0001$). The median PFS was 4.4 months and 2.86 months, respectively, and the ORR was 28% for ramucirumab plus paclitaxel compared with 6% for paclitaxel alone ($P=.0001$). Neutropenia and hypertension were more common with ramucirumab plus paclitaxel. An exposure-response analysis revealed that ramucirumab was a significant predictor of OS and PFS in both studies.¹⁵⁴ Based on these results, ramucirumab (as a single agent or in combination with paclitaxel) was approved by the FDA for the treatment of patients with advanced gastric or EGJ adenocarcinoma refractory to or progressive after first-line therapy with platinum- or fluoropyrimidine-based chemotherapy. The guidelines recommend ramucirumab as a single agent (category 1) or in combination with paclitaxel (category 1; preferred) as treatment options for second-line or subsequent therapy in patients with advanced or metastatic gastric adenocarcinoma.^{124,125}

Ramucirumab combined with FOLFIRI can be an option for second-line or subsequent therapy. In a multi-institutional retrospective analysis of 29 patients with advanced gastric or EGJ adenocarcinoma who received FOLFIRI plus ramucirumab in the second-line setting, the ORR was 23% with a disease control rate of 79%.¹³⁹ Median PFS was 6 months, and median OS was 13.4 months. Six- and 12-month OS were 90% and 41%, respectively. No new

safety signals were observed with the combination treatment, making FOLFIRI plus ramucirumab a safe, nonneurotoxic alternative to ramucirumab plus paclitaxel. Ramucirumab combined with irinotecan is also an option for second-line or subsequent therapy for patients with advanced gastric cancer.¹³⁸

Due to the results of the international phase III RAINFALL trial, in which treatment with ramucirumab did not reduce the risk of disease progression or death in treatment-naïve patients with metastatic gastroesophageal adenocarcinoma, the addition of ramucirumab to first-line chemotherapy is not recommended at this time.¹⁵⁵

Nivolumab

Nivolumab is a monoclonal PD-1 antibody that was approved by the FDA in April 2021, in combination with fluoropyrimidine- and platinum-based chemotherapy, for the first-line treatment of patients with advanced or metastatic gastric cancer.¹⁵⁶ This approval was based on results from the phase III Checkmate-649 trial, which randomized 1581 patients with previously untreated, HER2 negative unresectable gastric, EGJ or esophageal adenocarcinoma to receive chemotherapy alone or nivolumab plus chemotherapy (capecitabine and oxaliplatin or modified FOLFOX).⁸⁰ The addition of nivolumab to chemotherapy resulted in significant improvements in OS (14.4 vs 11.1 months; HR=0.71; $P<.0001$) and PFS (7.7 vs 6 months; HR=0.68; $P<.0001$) compared with chemotherapy alone in patients with a PD-L1 CPS of ≥ 5 (n=955). Additional results also showed some improvement in OS and PFS in patients with a PD-L1 CPS of ≥ 1 (n=1,296; OS=14 vs 11.3 months, HR=0.77; PFS=7.5 vs 6.9, HR=0.74) and in all randomly assigned patients (OS=13.8 vs 11.6, HR=0.8; PFS=7.7 vs 6.9, HR=0.77). Among all patients, 59% of those in the nivolumab plus chemotherapy group and 44% of those in the chemotherapy alone group experienced grade 3-4 treatment-related adverse events. The most common any-grade treatment-related adverse events were nausea, diarrhea, and peripheral neuropathy across both groups. Sixteen treatment-related deaths occurred in the nivolumab plus chemotherapy group compared with 4 in the chemotherapy alone group. Therefore, nivolumab plus fluoropyrimidine- and oxaliplatin-based chemotherapy is a preferred first-line treatment option for patients with HER2 negative gastric tumors with PD-L1 expression levels by CPS of ≥ 5 (category 1) and is useful under certain circumstances for tumors with PD-L1 expression levels by CPS of <5 (category 2B).

Pembrolizumab

Pembrolizumab is a PD-1 antibody that was FDA approved in 2017 for the treatment of patients with unresectable or

metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.¹⁵⁷ This first-ever tissue- and site-agnostic approval was based on data from 149 patients with MSI-H/dMMR cancers (90 patients had colorectal cancer) enrolled across 5 multicenter single-arm clinical trials.^{65,141,142} The ORR was 39.6% and responses lasted ≥ 6 months for 78% of those who responded to pembrolizumab. There were 11 complete responses and 48 partial responses, and the ORR was similar irrespective of cancer type.

In June 2020, the FDA approved pembrolizumab for the treatment of patients with metastatic TMB-H solid tumors, as determined by an FDA-approved test, that have progressed after prior treatment and who have no satisfactory alternative treatment options.¹⁵⁸ This approval was based on a retrospective analysis of 102 patients enrolled in the KEYNOTE-158 trial who had tumors identified as TMB-H.¹⁴⁴ The ORR for these patients was 29%, with a 4% complete response rate. The median duration of response was not reached, with 50% of patients having response durations for ≥ 24 months. Based on these data, pembrolizumab may be used for the second-line or subsequent treatment of MSI-H/dMMR or TMB-H gastroesophageal tumors. However, it should be noted that no patients with gastroesophageal cancer were included in the KEYNOTE-158 trial.

Additional trials of pembrolizumab in gastric and EGJ cancers are ongoing. Please visit <https://keynoteclinicaltrials.com> for more information regarding ongoing KEYNOTE clinical trials for pembrolizumab in patients with gastric and EGJ cancers.

Dostarlimab-gxly

Dostarlimab-gxly, an anti-PD-1 antibody, was approved by the FDA in August 2021 for the treatment of patients with dMMR recurrent or advanced solid tumors that have progressed on or after prior treatment, who have no satisfactory alternative treatment options, and who had not previously received a PD-1 or PD-L1 inhibitor.¹⁵⁹ This approval was based on data from the nonrandomized phase 1 multicohort GARNET trial that evaluated the safety and antitumor activity of dostarlimab-gxly in 209 patients with dMMR solid tumors who had not received prior PD-1, PDL-1, or CTLA4 inhibitors.^{143,160} The majority of patients had endometrial or gastrointestinal cancers. The ORR was 42%, with a 9% complete response rate and 33% partial response rate, and the median duration of response was 35 months. The most common treatment-related adverse events were fatigue, anemia, diarrhea, and nausea. Immune-mediated adverse events also occurred, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, and dermatologic toxicities.

Based on these data, dostarlimab-gxly may be used to treat patients with MSI-H/dMMR gastric tumors.

Entrectinib and Larotrectinib

Gene fusions involving *NTRK1*, *NTRK2*, or *NTRK3* encode TRK fusion proteins (TRKA, TRKB, TRKC), which have increased kinase function and are implicated in the oncogenesis of many solid tumors including head and neck, thyroid, soft tissue, lung, and colon.^{146,161} Although believed to be extremely rare in gastroesophageal cancers, one case report provides evidence that *NTRK* gene fusions do occur in gastric adenocarcinoma and may be associated with an aggressive phenotype.^{162–164}

In 2018, the FDA granted accelerated approval to the TRK inhibitor larotrectinib for the treatment of adult and pediatric patients (aged 12 years and older) with solid tumors that have an *NTRK* gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed after treatment.¹⁵⁰ This second-ever tissue-agnostic FDA approval for the treatment of patients with cancer was based on data from 3 multicenter single-arm clinical trials. Patients with prospectively identified *NTRK* gene fusion-positive cancers were enrolled into 1 of 3 protocols: a phase I trial involving adults (LOXO-TRK-14001), a phase I–II trial involving children (SCOUT), and a phase II trial involving adolescents and adults (NAVIGATE).¹⁴⁶ A total of 55 patients with unresectable or metastatic solid tumors harboring an *NTRK* gene fusion who experienced disease progression after systemic therapy were enrolled across the 3 trials and treated with larotrectinib. The most common cancer types represented were salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%), and thyroid cancer (9%). The ORR across the 3 trials was 75%, with a complete response rate of 22%. At a median follow-up of 9.4 months, 86% of the patients with a response were either continuing treatment with larotrectinib or had undergone curative-intent surgery. At 1 year, 71% of the responses were ongoing and 55% of the patients remained progression-free. Response duration was ≥ 6 months for 73%, ≥ 9 months for 63%, and ≥ 12 months for 39% of patients. At the time of data analysis, the median duration of response and PFS had not been reached. Adverse events were predominantly grade 1, the most common being increased aspartate aminotransferase (AST) levels, vomiting, constipation, and dizziness. The SCOUT (ClinicalTrials.gov identifier: NCT02637687) and NAVIGATE (ClinicalTrials.gov identifier: NCT02576431) trials are still actively recruiting patients with *NTRK* gene fusion-positive tumors.

In 2019, the FDA approved the second TRK inhibitor, entrectinib, for the same indications as larotrectinib, as well as for adult patients with metastatic non-small cell lung cancer whose tumors are *ROS1*-positive.¹⁴⁹ The approval of entrectinib for the treatment of *NTRK* gene fusion-positive tumors was based on data from 3 multicenter single-arm phase I and phase II clinical trials. A total of 54 patients aged 18 years or older with metastatic or locally advanced *NTRK* gene fusion-positive solid tumors were enrolled into 1 of the 3 protocols (ALKA-372-001, STARTRK-1, and STARTRK-2).¹⁴⁵ The most common cancer types represented were sarcoma, non-small cell lung cancer, mammary analogue secretory carcinoma, breast, thyroid, and colorectal. The ORR across the 3 trials was 57%, with a complete response rate of 7%. Response duration was ≥ 6 months for 68% of patients and ≥ 12 months for 45% of patients. The median duration of response was 10 months. The most common grade 3–4 treatment-related adverse events were increased weight and anemia while the most common serious treatment-related adverse events were nervous system disorders. STARTRK-2 (ClinicalTrials.gov identifier: NCT02568267) is still actively recruiting patients with *NTRK* gene fusion-positive tumors.

These data demonstrate that entrectinib and larotrectinib induce durable and clinically meaningful responses in patients with *NTRK* gene fusion-positive tumors with manageable safety profiles. Therefore, entrectinib and larotrectinib are recommended as second-line or subsequent treatment options for patients with *NTRK* gene fusion-positive gastric tumors.

Palliative/Best Supportive Care

The goals of palliative/best supportive care are to prevent, reduce, and relieve suffering and improve the quality of life for patients and their caregivers, regardless of the stage of the disease or the need for other therapies. In patients with advanced or metastatic gastric cancer, palliative/best supportive care provides symptom relief, improvement in overall quality of life, and may result in prolongation of life. This is especially true when a multimodality interdisciplinary approach is pursued. Therefore, a multimodality interdisciplinary approach to palliative/best supportive care of gastric cancer patients is encouraged.

Bleeding

Acute bleeding is common in patients with gastric cancer and may be tumor-related or a consequence of therapy. Patients with acute severe bleeding (hematemesis or melena) should undergo prompt endoscopic assessment (see GAST-J 1 of 3, page 179).¹⁶⁵ The efficacy of endoscopic treatment of bleeding in patients with gastric cancer is not well-studied, but limited available data suggest

that while endoscopic therapies may be effective as initial treatment, the rate of recurrent bleeding is very high.^{166,167} Widely available options for endoscopic therapies include injection therapy, mechanical therapy (eg, endoscopic clip placement), ablative therapy (eg, argon plasma coagulation or other laser therapy), or a combination of modalities.¹⁶⁶ Interventional radiology with angiographic embolization techniques may be useful in situations where endoscopy is not helpful.¹⁶⁸ Additionally, external beam radiation therapy (EBRT) has been shown to effectively manage acute and chronic gastrointestinal bleeding.^{169,170} Proton pump inhibitors can also be prescribed to reduce the risk of bleeding from gastric cancer; however, there are no definitive data supporting their use at this time.

Obstruction

The primary goals of palliation for patients with malignant gastric obstruction are to reduce nausea and vomiting and, when possible, allow resumption of an oral diet (see GAST-J 2 of 3, page 180). Management of malignant gastric obstruction should be individualized, and treatment options selected as clinically appropriate. Treatment options used to alleviate or bypass obstruction include surgery (gastrojejunostomy¹⁷¹ or gastrectomy in select patients¹⁷²), EBRT, chemotherapy, and endoscopic placement of an enteral stent for relief of gastric outlet obstruction¹⁷¹ or esophageal stent for EGJ/cardia obstruction. Endoscopic placement of a self-expanding metal stent (SEMS) is a safe and effective minimally invasive palliative treatment of patients with luminal obstruction due to advanced gastric cancer.^{173–176} In a systematic review, patients treated with endoscopic placement of a SEMS were more likely to tolerate oral intake and had shorter hospital stays than patients treated with gastrojejunostomy.¹⁷⁷ The results of another systematic review suggest that SEMS placement may be associated with more favorable results in patients with a relatively short life expectancy, whereas gastrojejunostomy is preferable in patients with a more prolonged prognosis.¹⁷¹ A randomized trial also reported similar findings.¹⁷⁸ However, these results need to be confirmed in larger randomized trials.

When obstruction cannot be alleviated or bypassed, the primary goal is to reduce the symptoms of obstruction via venting gastrostomy.¹⁷⁹ Percutaneous, endoscopic, surgical, or interventional radiology gastrostomy tube placement may be performed for gastric decompression, if tumor location permits. Percutaneous decompressive gastrostomy has been associated with palliative benefit for patients with gastric outlet obstruction.^{180,181} Ascites, if present, should be drained before venting gastrostomy tube placement to reduce the risk of infectious complications.^{182,183} Feeding gastrostomy tubes for patients with EGJ/gastric cardia obstruction or jejunal feeding tubes

for patients with mid and distal gastric obstruction may be necessary to provide adequate hydration and nutritional support for patients who cannot tolerate an oral diet. Nutritional counseling may also be valuable.

Pain

Pain control may be achieved with the use of EBRT or chemotherapy (see GAST-J 2 of 3, page 180). If the patient is experiencing tumor-related pain, then pain should be assessed and treated according to the NCCN Guidelines for Adult Cancer Pain (available at NCCN.org). Severe, uncontrolled pain after gastric stent placement should be treated with immediate endoscopic removal of the stent.

Nausea and Vomiting

Patients experiencing nausea and vomiting should be treated according to the NCCN Guidelines for Antiemesis (see GAST-J 2 of 3, page 180). Nausea and vomiting may be associated with luminal obstruction, so endoscopic or fluoroscopic evaluation should be performed to determine if obstruction is present.

Summary

Gastric cancer is rampant in many parts of the world and is often diagnosed at advanced stages. Risk factors for gastric cancer include *H pylori* infection, smoking, and high salt intake. Some gastric cancers are associated with inherited gastric cancer predisposition syndromes. Referral to a cancer genetics professional is recommended for an individual with a genetic predisposition. The NCCN

Guidelines for Gastric Cancer provide an evidence- and consensus-based treatment approach for the management of patients with gastric cancer. Multidisciplinary team management is essential for the management of patients with gastric cancer. Best supportive care is an integral part of treatment, especially in patients with unresectable locally advanced, recurrent, or metastatic disease. Patients with unresectable or metastatic disease may be offered best supportive care and palliative management with or without systemic therapy or chemoradiation, depending on their performance status and prior treatment. Targeted therapies have produced encouraging results in the treatment of patients with advanced gastric cancer. Trastuzumab plus chemotherapy is recommended as first-line therapy for patients with HER2 overexpression-positive tumors. Nivolumab combined with chemotherapy is recommended as first-line therapy for tumors with PD-L1 expression levels by CPS of ≥ 5 (category 1) or CPS of < 5 (category 2B). Ramucirumab, as a single agent or in combination with paclitaxel (preferred), and pembrolizumab (for MSI-H/dMMR or TMB-H tumors) are included as options for second-line or subsequent therapy for patients with metastatic gastric cancer. Dostarlimab-glyx is an alternative option to pembrolizumab for MSI-H/dMMR tumors. Entrectinib and larotrectinib are recommended for second-line or subsequent therapy for *NTRK* gene fusion-positive tumors. The panel encourages patients with gastric cancer to participate in well-designed clinical trials investigating novel therapeutic strategies to enable further advances.

References

- Sitarz R, Skierucha M, Mielko J, et al. Gastric cancer: epidemiology, prevention, classification, and treatment. *Cancer Manag Res* 2018;10:239–248.
- Crew KD, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006;12:354–362.
- Ma J, Shen H, Kapesa L, et al. Lauren classification and individualized chemotherapy in gastric cancer. *Oncol Lett* 2016;11:2959–2964.
- National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Stat Facts: Stomach Cancer. 2021. Accessed July 9, 2021. Available at: <https://seer.cancer.gov/statfacts/html/stomach.html>
- Torre LA, Siegel RL, Ward EM, et al. Global cancer incidence and mortality rates and trends—an update. *Cancer Epidemiol Biomarkers Prev* 2016;25:16–27.
- Etemadi A, Safiri S, Sepanlou SG, et al. The global, regional, and national burden of stomach cancer in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease study 2017. *Lancet Gastroenterol Hepatol* 2020;5:42–54.
- Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.
- World Health Organization. International Agency for Research on Cancer. GLOBOCAN 2020: stomach cancer fact sheet. 2020. Accessed July 9, 2021. Available at: <https://gco.iarc.fr/today/data/factsheets/cancers/7-Stomach-fact-sheet.pdf>
- Zhao JK, Wu M, Kim CH, et al. Jiangsu Four Cancers Study: a large case-control study of lung, liver, stomach, and esophageal cancers in Jiangsu Province, China. *Eur J Cancer Prev* 2017;26:357–364.
- Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. *CA Cancer J Clin* 2021;71:7–33.
- World Health Organization. International Agency for Research on Cancer. GLOBOCAN 2020: United States of America cancer fact sheet. 2020. Accessed July 9, 2021. Available at: <http://gco.iarc.fr/today/data/factsheets/populations/840-united-states-of-america-fact-sheets.pdf>
- Bergquist JR, Leiting JL, Habermann EB, et al. Early-onset gastric cancer is a distinct disease with worrisome trends and oncogenic features. *Surgery* 2019;166:547–555.
- Karimi P, Islami F, Anandasabapathy S, et al. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. *Cancer Epidemiol Biomarkers Prev* 2014;23:700–713.
- Yusefi AR, Bagheri Lankarani K, Bastani P, et al. Risk factors for gastric cancer: a systematic review. *Asian Pac J Cancer Prev* 2018;19:591–603.
- Hu B, El Hajj N, Sittler S, et al. Gastric cancer: classification, histology and application of molecular pathology. *J Gastrointest Oncol* 2012;3:251–261.
- Tramacere I, Negri E, Pelucchi C, et al. A meta-analysis on alcohol drinking and gastric cancer risk. *Ann Oncol* 2012;23:28–36.
- He Z, Zhao TT, Xu HM, et al. Association between alcohol consumption and the risk of gastric cancer: a meta-analysis of prospective cohort studies. *Oncotarget* 2017;8:84459–84472.
- Wang PL, Xiao FT, Gong BC, et al. Alcohol drinking and gastric cancer risk: a meta-analysis of observational studies. *Oncotarget* 2017;8:99013–99023.
- Deng W, Jin L, Zhuo H, et al. Alcohol consumption and risk of stomach cancer: a meta-analysis. *Chem Biol Interact* 2021;336:109365.

20. Falk J, Carstens H, Lundell L, et al. Incidence of carcinoma of the oesophagus and gastric cardia. Changes over time and geographical differences. *Acta Oncol* 2007;46:1070–1074.
21. Powell J, McConkey CC, Gillison EW, et al. Continuing rising trend in oesophageal adenocarcinoma. *Int J Cancer* 2002;102:422–427.
22. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC cancer staging manual*, 8th Ed. New York, NY: Springer; 2017.
23. Bando E, Makuuchi R, Irino T, et al. Validation of the prognostic impact of the new tumor-node-metastasis clinical staging in patients with gastric cancer. *Gastric Cancer* 2019;22:123–129.
24. Sano T, Coit DG, Kim HH, et al. Proposal of a new stage grouping of gastric cancer for TNM classification: International Gastric Cancer Association staging project. *Gastric Cancer* 2017;20:217–225.
25. In H, Solsky I, Palis B, et al. Validation of the 8th edition of the AJCC TNM staging system for gastric cancer using the National Cancer Database. *Ann Surg Oncol* 2017;24:3683–3691.
26. Huang SF, Chien TH, Fang WL, et al. The 8th edition American Joint Committee on gastric cancer pathological staging classification performs well in a population with high proportion of locally advanced disease. *Eur J Surg Oncol* 2018;44:1634–1639.
27. Abdalla EK, Pisters PWT. Staging and preoperative evaluation of upper gastrointestinal malignancies. *Semin Oncol* 2004;31:513–529.
28. Kwee RM, Kwee TC. Imaging in local staging of gastric cancer: a systematic review. *J Clin Oncol* 2007;25:2107–2116.
29. Weber WA, Ott K. Imaging of esophageal and gastric cancer. *Semin Oncol* 2004;31:530–541.
30. Matsumoto Y, Yanai H, Tokiyama H, et al. Endoscopic ultrasonography for diagnosis of submucosal invasion in early gastric cancer. *J Gastroenterol* 2000;35:326–331.
31. Cardoso R, Coburn N, Seevaratnam R, et al. A systematic review and meta-analysis of the utility of EUS for preoperative staging for gastric cancer. *Gastric Cancer* 2012; 15(S1, Suppl 1):S19–S26.
32. Spolverato G, Ejaz A, Kim Y, et al. Use of endoscopic ultrasound in the preoperative staging of gastric cancer: a multi-institutional study of the US gastric cancer collaborative. *J Am Coll Surg* 2015;220:48–56.
33. Tsenduren T, Jun S-M, Mian X-H. Usefulness of endoscopic ultrasonography in preoperative TNM staging of gastric cancer. *World J Gastroenterol* 2006;12:43–47.
34. Stahl A, Ott K, Weber WA, et al. FDG PET imaging of locally advanced gastric carcinomas: correlation with endoscopic and histopathological findings. *Eur J Nucl Med Mol Imaging* 2003;30:288–295.
35. Wieder HA, Krause BJ, Hermann K. PET and PET-CT in esophageal and gastric cancer. *Methods Mol Biol* 2011;727:59–76.
36. Chen J, Cheong J-H, Yun MJ, et al. Improvement in preoperative staging of gastric adenocarcinoma with positron emission tomography. *Cancer* 2005;103:2383–2390.
37. Rosenbaum SJ, Stergar H, Antoch G, et al. Staging and follow-up of gastrointestinal tumors with PET/CT. *Abdom Imaging* 2006;31:25–35.
38. Dassen AE, Lips DJ, Hoekstra CJ, et al. FDG-PET has no definite role in preoperative imaging in gastric cancer. *Eur J Surg Oncol* 2009;35:449–455.
39. Lim JS, Yun MJ, Kim M-J, et al. CT and PET in stomach cancer: preoperative staging and monitoring of response to therapy. *Radiographics* 2006;26:143–156.
40. Sarela AI, Lefkowitz R, Brennan MF, et al. Selection of patients with gastric adenocarcinoma for laparoscopic staging. *Am J Surg* 2006;191:134–138.
41. Bentrem D, Wilton A, Mazumdar M, et al. The value of peritoneal cytology as a preoperative predictor in patients with gastric carcinoma undergoing a curative resection. *Ann Surg Oncol* 2005;12:347–353.
42. Mezhir JJ, Shah MA, Jacks LM, et al. Positive peritoneal cytology in patients with gastric cancer: natural history and outcome of 291 patients. *Ann Surg Oncol* 2010;17:3173–3180.
43. De Andrade JP, Mezhir JJ. The critical role of peritoneal cytology in the staging of gastric cancer: an evidence-based review. *J Surg Oncol* 2014;110:291–297.
44. Chau I, Norman AR, Cunningham D, et al. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer-pooled analysis from three multicenter, randomized, controlled trials using individual patient data. *J Clin Oncol* 2004;22:2395–2403.
45. Karpeh MS, Leon L, Klimstra D, et al. Lymph node staging in gastric cancer: is location more important than number? An analysis of 1,038 patients. *Ann Surg* 2000;232:362–371.
46. Hechtman JF, Polydorides AD. HER2/neu gene amplification and protein overexpression in gastric and gastroesophageal junction adenocarcinoma: a review of histopathology, diagnostic testing, and clinical implications. *Arch Pathol Lab Med* 2012;136:691–697.
47. Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. *Ann Oncol* 2008;19:1523–1529.
48. Chua TC, Merrett ND. Clinicopathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes—a systematic review. *Int J Cancer* 2012;130:2845–2856.
49. Gómez-Martin C, Garralda E, Echarri MJ, et al. HER2/neu testing for anti-HER2-based therapies in patients with unresectable and/or metastatic gastric cancer. *J Clin Pathol* 2012;65:751–757.
50. Jørgensen JT, Hersom M. HER2 as a prognostic marker in gastric cancer - a systematic analysis of data from the literature. *J Cancer* 2012;3:137–144.
51. Kato S, Okamura R, Baumgartner JM, et al. Analysis of circulating tumor DNA and clinical correlates in patients with esophageal, gastroesophageal junction, and gastric adenocarcinoma. *Clin Cancer Res* 2018;24:6248–6256.
52. Cho JH, Lim JY, Cho JY. Survival analysis based on human epidermal growth factor 2 status in stage II-III gastric cancer. *World J Gastroenterol* 2017;23:7407–7414.
53. Grabsch H, Sivakumar S, Gray S, et al. HER2 expression in gastric cancer: rare, heterogeneous and of no prognostic value - conclusions from 924 cases of two independent series. *Cell Oncol* 2010;32:57–65.
54. Janjigian YY, Werner D, Pauligk C, et al. Prognosis of metastatic gastric and gastroesophageal junction cancer by HER2 status: a European and USA international collaborative analysis. *Ann Oncol* 2012;23:2656–2662.
55. Kunz PL, Mojtabeh A, Fisher GA, et al. HER2 expression in gastric and gastroesophageal junction adenocarcinoma in a US population: clinicopathologic analysis with proposed approach to HER2 assessment. *Appl Immunohistochem Mol Morphol* 2012;20:13–24.
56. Tanner M, Holmén M, Junttila TT, et al. Amplification of HER-2 in gastric carcinoma: association with topoisomerase IIalpha gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. *Ann Oncol* 2005;16:273–278.
57. Yan B, Yau EX, Bte Omar SS, et al. A study of HER2 gene amplification and protein expression in gastric cancer. *J Clin Pathol* 2010;63:839–842.
58. Kim WH, Gomez-Izquierdo L, Vilardell F, et al. HER2 status in gastric and gastroesophageal junction cancer: results of the large, multinational HER-EAGLE study. *Appl Immunohistochem Mol Morphol* 2018;26:239–245.
59. Van Cutsem E, Bang YJ, Feng-Yi F, et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. *Gastric Cancer* 2015;18:476–484.
60. 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;376:687–697.
61. Bartley AN, Washington MK, Colasacco C, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. *J Clin Oncol* 2017;35:446–464.
62. Hofmann M, Stoss O, Shi D, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. *Histopathology* 2008;52:797–805.
63. Rüschhoff J, Dietel M, Baretton G, et al. HER2 diagnostics in gastric cancer-guideline validation and development of standardized immunohistochemical testing. *Virchows Arch* 2010;457:299–307.
64. Murphy KM, Zhang S, Geiger T, et al. Comparison of the microsatellite instability analysis system and the Bethesda panel for the determination of microsatellite instability in colorectal cancers. *J Mol Diagn* 2006;8:305–311.
65. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017;357:409–413.
66. Bartley AN, Fitzgibbons PL, Broaddus RR, et al. Template for reporting results of DNA mismatch repair testing in patients being considered for checkpoint inhibitor immunotherapy. Northfield, IL: College of American Pathologists; 2018.
67. Willis J, Lefterova MI, Artyomenko A, et al. Validation of microsatellite instability detection using a comprehensive plasma-based genotyping panel. *Clin Cancer Res* 2019;25:7035–7045.

68. Brar SS, Mahar AL, Helyer LK, et al. Processes of care in the multidisciplinary treatment of gastric cancer: results of a RAND/UCLA expert panel. *JAMA Surg* 2014;149:18–25.
69. Siewert JR. Carcinoma of the cardia: carcinoma of the gastroesophageal junction classification, pathology, and extent of resection. *Dis Esophagus* 1996;9:173–182.
70. Rüdiger Siewert J, Feith M, Werner M, et al. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. *Ann Surg* 2000;232:353–361.
71. MacLeod CM, ed. The clinical evaluation of chemotherapeutic agents in cancer. In: *Evaluation of Chemotherapeutic Agents*. New York, NY: Columbia University Press; 1949.
72. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–655.
73. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. *J Clin Oncol* 1984;2:187–193.
74. Glimelius B, Ekström K, Hoffman K, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997;8:163–168.
75. Thuss-Patience PC, Kretschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer—a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer* 2011;47:2306–2314.
76. Kang JH, Lee SI, Lim DH, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 2012;30:1513–1518.
77. Ford HE, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol* 2014;15:78–86.
78. Al-Batran SE, Pauligk C, Homann N, et al. The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65+). *Eur J Cancer* 2013;49:835–842.
79. Chung HC, Bang YJ, Fuchs CS, et al. First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer: KEYNOTE-811. *Future Oncol* 2021;17:491–501.
80. 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;398:27–40.
81. Al-Batran S-E, 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* 2008;26:1435–1442.
82. Enzinger PC, Burtness BA, Niedzwiecki D, et al. CALGB 80403 (Alliance)/E1206: a randomized phase II study of three chemotherapy regimens plus cetuximab in metastatic esophageal and gastroesophageal junction cancers. *J Clin Oncol* 2016;34:2736–2742.
83. Kim GM, Jeung HC, Rha SY, et al. A randomized phase II trial of S-1-oxaliplatin versus capecitabine-oxaliplatin in advanced gastric cancer. *Eur J Cancer* 2012;48:518–526.
84. Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. *Ann Oncol* 2009;20:1667–1673.
85. Bouché O, Raoul JL, Bonnetain F, et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study-FFCD 9803. *J Clin Oncol* 2004;22:4319–4328.
86. Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol* 2009;20:666–673.
87. Louvet C, André T, Tigaud JM, et al. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. *J Clin Oncol* 2002;20:4543–4548.
88. Al-Batran S-E, Atmaca A, Hegewisch-Becker S, et al. Phase II trial of biweekly infusional fluorouracil, folinic acid, and oxaliplatin in patients with advanced gastric cancer. *J Clin Oncol* 2004;22:658–663.
89. Park YH, Lee JL, Ryoo BY, et al. Capecitabine in combination with oxaliplatin (XELOX) as a first-line therapy for advanced gastric cancer. *Cancer Chemother Pharmacol* 2008;61:623–629.
90. Luo HY, Xu RH, Wang F, et al. Phase II trial of XELOX as first-line treatment for patients with advanced gastric cancer. *Chemotherapy* 2010;56:94–100.
91. Okines AFC, Norman AR, McCloud P, et al. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. *Ann Oncol* 2009;20:1529–1534.
92. Wang G, Yang B, Fu Z, et al. Efficacy and safety of oxaliplatin-based regimen versus cisplatin-based regimen in the treatment of gastric cancer: a meta-analysis of randomized controlled trials. *Int J Clin Oncol* 2019;24:614–623.
93. Hall PS, Swinson D, Waters JS, et al. Optimizing chemotherapy for frail and elderly patients (pts) with advanced gastroesophageal cancer (aGOAC): the GO2 phase III trial. *J Clin Oncol* 2019;37(15_suppl):4006.
94. Enzinger PC, Kulke MH, Clark JW, et al. A phase II trial of irinotecan in patients with previously untreated advanced esophageal and gastric adenocarcinoma. *Dig Dis Sci* 2005;50:2218–2223.
95. Ajani JA, Baker J, Pisters PWT, et al. CPT-11 plus cisplatin in patients with advanced, untreated gastric or gastroesophageal junction carcinoma: results of a phase II study. *Cancer* 2002;94:641–646.
96. Moehler M, Haas U, Siebler J, et al. Weekly treatment with irinotecan, folinic acid and infusional 5-fluorouracil (ILF) in patients with advanced gastric cancer. *Anticancer Drugs* 2003;14:645–650.
97. Pozzo C, Barone C, Szanto J, et al. Irinotecan in combination with 5-fluorouracil and folinic acid or with cisplatin in patients with advanced gastric or esophageal-gastric junction adenocarcinoma: results of a randomized phase II study. *Ann Oncol* 2004;15:1773–1781.
98. Moehler M, Eimermacher A, Siebler J, et al. Randomised phase II evaluation of irinotecan plus high-dose 5-fluorouracil and leucovorin (ILF) vs 5-fluorouracil, leucovorin, and etoposide (ELF) in untreated metastatic gastric cancer. *Br J Cancer* 2005;92:2122–2128.
99. Beretta E, Di Bartolomeo M, Buzzoni R, et al. Irinotecan, fluorouracil and folinic acid (FOLFIRI) as effective treatment combination for patients with advanced gastric cancer in poor clinical condition. *Tumori* 2006;92:379–383.
100. Dank M, Zaluski J, Barone C, et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. *Ann Oncol* 2008;19:1450–1457.
101. Brell JM, Krishnamurthy SS, Javle M, et al. A multi-center phase II study of oxaliplatin, irinotecan, and capecitabine in advanced gastric/gastroesophageal junction carcinoma. *Cancer Chemother Pharmacol* 2009;63:851–857.
102. Enzinger PC, Ryan DP, Clark JW, et al. Weekly docetaxel, cisplatin, and irinotecan (TPC): results of a multicenter phase II trial in patients with metastatic esophagogastric cancer. *Ann Oncol* 2009;20:475–480.
103. Lustberg MB, Bekaii-Saab T, Young D, et al. Phase II randomized study of two regimens of sequentially administered mitomycin C and irinotecan in patients with unresectable esophageal and gastroesophageal adenocarcinoma. *J Thorac Oncol* 2010;5:713–718.
104. Moehler M, Kanzler S, Geissler M, et al. A randomized multicenter phase II study comparing capecitabine with irinotecan or cisplatin in metastatic adenocarcinoma of the stomach or esophagogastric junction. *Ann Oncol* 2010;21:71–77.
105. Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French intergroup (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) study. *J Clin Oncol* 2014;32:3520–3526.
106. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006;24:4991–4997.
107. Roth AD, Fazio N, Stupp R, et al. Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. *J Clin Oncol* 2007;25:3217–3223.

108. Al-Batran SE, Hartmann JT, Hofheinz R, et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. *Ann Oncol* 2008;19:1882–1887.
109. Elsaid AA, Elkerm Y. Final results of a randomized phase III trial of docetaxel, carboplatin and 5FU versus epirubicin, cisplatin and 5FU for locally advanced gastric cancer. *J Clin Oncol* 2005;23(16_suppl):4014.
110. Inal A, Kaplan MA, Kucukoner M, et al. Docetaxel and cisplatin plus fluorouracil compared with modified docetaxel, cisplatin, and 5-fluorouracil as first-line therapy for advanced gastric cancer: a retrospective analysis of single institution. *Neoplasma* 2012;59:233–236.
111. Di Lauro L, Vici P, Belli F, et al. Docetaxel, oxaliplatin, and capecitabine combination chemotherapy for metastatic gastric cancer. *Gastric Cancer* 2014;17:718–724.
112. Van Cutsem E, Boni C, Tabernero J, et al. Docetaxel plus oxaliplatin with or without fluorouracil or capecitabine in metastatic or locally recurrent gastric cancer: a randomized phase II study. *Ann Oncol* 2015;26:149–156.
113. Shah MA, Janjigian YY, Stoller R, et al. Randomized multicenter phase II study of modified docetaxel, cisplatin, and fluorouracil (DCF) versus DCF plus growth factor support in patients with metastatic gastric adenocarcinoma: a study of the US Gastric Cancer Consortium. *J Clin Oncol* 2015;33:3874–3879.
114. Ilson DH, Forastiere A, Arquette M, et al. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. *Cancer J* 2000;6:316–323.
115. Petrasch S, Welt A, Reinacher A, et al. Chemotherapy with cisplatin and paclitaxel in patients with locally advanced, recurrent or metastatic oesophageal cancer. *Br J Cancer* 1998;78:511–514.
116. Gadgil SM, Shields AF, Heilbrun LK, et al. Phase II study of paclitaxel and carboplatin in patients with advanced gastric cancer. *Am J Clin Oncol* 2003;26:37–41.
117. Ajani JA, Fodor MB, Tjulandin SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. *J Clin Oncol* 2005;23:5660–5667.
118. Kim JY, Do YR, Park KU, et al. A multi-center phase II study of docetaxel plus cisplatin as first-line therapy in patients with metastatic squamous cell esophageal cancer. *Cancer Chemother Pharmacol* 2010;66:31–36.
119. Ohtsu A, Shimada Y, Shirao K, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: the Japan Clinical Oncology Group Study (JCOG9205). *J Clin Oncol* 2003;21:54–59.
120. Hong YS, Song SY, Lee SI, et al. A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. *Ann Oncol* 2004;15:1344–1347.
121. Albertsson M, Johansson B, Friesland S, et al. Phase II studies on docetaxel alone every third week, or weekly in combination with gemcitabine in patients with primary locally advanced, metastatic, or recurrent esophageal cancer. *Med Oncol* 2007;24:407–412.
122. Ajani JA, Ilson DH, Daugherty K, et al. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. *J Natl Cancer Inst* 1994;86:1086–1091.
123. Ilson DH, Wadleigh RG, Leichman LP, et al. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. *Ann Oncol* 2007;18:898–902.
124. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014;383:31–39.
125. 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;15:1224–1235.
126. Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med* 2020;382:2419–2430.
127. Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. *J Clin Oncol* 2013;31:4438–4444.
128. Fuchs CS, Moore MR, Harker G, et al. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. *J Clin Oncol* 2003;21:807–814.
129. Sym SJ, Hong J, Park J, et al. A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. *Cancer Chemother Pharmacol* 2013;71:481–488.
130. Maugeri-Saccà M, Pizzuti L, Sergi D, et al. FOLFIRI as a second-line therapy in patients with docetaxel-pretreated gastric cancer: a historical cohort. *J Exp Clin Cancer Res* 2013;32:67.
131. Sym SJ, Ryu MH, Lee JL, et al. Salvage chemotherapy with biweekly irinotecan, plus 5-fluorouracil and leucovorin in patients with advanced gastric cancer previously treated with fluoropyrimidine, platinum, and taxane. *Am J Clin Oncol* 2008;31:151–156.
132. Assersohn L, Brown G, Cunningham D, et al. Phase II study of irinotecan and 5-fluorouracil/leucovorin in patients with primary refractory or relapsed advanced oesophageal and gastric carcinoma. *Ann Oncol* 2004;15:64–69.
133. U.S. Food and Drug Administration. FDA approves Lonsurf for recurrent, metastatic gastric and gastroesophageal junction adenocarcinoma. 2019. Available at: <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm632032.htm>. Accessed March 6, 2020.
134. 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.
135. Ilson DH, Tabernero J, Prokharau A, et al. Efficacy and safety of trifluridine/tipiracil treatment in patients with metastatic gastric cancer who had undergone gastrectomy: subgroup analyses of a randomized clinical trial. *JAMA Oncol* 2019;6:e193531.
136. Shitara K, Doi T, Hosaka H, et al. Trifluridine/tipiracil (FTD/TPI) in patients (pts) aged ≥65 years with metastatic gastric/gastroesophageal junction cancer (mGC/mGEJC): subgroup analysis from TAGS. *J Clin Oncol* 2019;37(15_suppl):4037.
137. Ilson DH. Phase II trial of weekly irinotecan/cisplatin in advanced esophageal cancer. *Oncology (Williston Park)* 2004; 18(14, Suppl 14):22–25.
138. Sakai D, Boku N, Koda Y, et al. An intergroup phase III trial of ramucirumab plus irinotecan in third or more line beyond progression after ramucirumab for advanced gastric cancer (RINDBERG trial). *J Clin Oncol* 2018;36(15_suppl):TPS4138.
139. Klemperer SJ, Maron SB, Chase L, et al. Initial report of second-line FOLFIRI in combination with ramucirumab in advanced gastroesophageal adenocarcinomas: a multi-institutional retrospective analysis. *Oncologist* 2019;24:475–482.
140. Burtenshaw B, Gibson M, Egleston B, et al. Phase II trial of docetaxel-irinotecan combination in advanced esophageal cancer. *Ann Oncol* 2009; 20:1242–1248.
141. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015;372:2509–2520.
142. 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;38:1–10.
143. Berton D, Banerjee SN, Curigliano G, et al. Antitumor activity of dostarlimab in patients with mismatch repair-deficient/microsatellite instability-high tumors: a combined analysis of two cohorts in the GARNET study. *J Clin Oncol* 2021;39(15_suppl):2564.
144. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol* 2020;21:1353–1365.
145. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol* 2020;21:271–282.
146. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med* 2018;378:731–739.
147. Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. *JAMA Oncol* 2018;4:e180013.
148. Le DT, Uram JN, Wang H, et al. PD-1 blockade in mismatch repair deficient non-colorectal gastrointestinal cancers. *J Clin Oncol* 2016; 34(4_suppl):195.

149. U.S. Food and Drug Administration. FDA approves entrectinib for NTRK solid tumors and ROS-1 NSCLC. 2019. Accessed July 14, 2020. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-entrectinib-ntrk-solid-tumors-and-ros-1-nsclc>
150. U.S. Food and Drug Administration. FDA approves larotrectinib for solid tumors with NTRK gene fusions. 2018. Accessed July 14, 2020. Available at: <https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions>
151. Rivera F, Romero C, Jimenez-Fonseca P, et al. Phase II study to evaluate the efficacy of trastuzumab in combination with capecitabine and oxaliplatin in first-line treatment of HER2-positive advanced gastric cancer: HERXO trial. *Cancer Chemother Pharmacol* 2019;83:1175–1181.
152. Soularue É, Cohen R, Tournigand C, et al. Efficacy and safety of trastuzumab in combination with oxaliplatin and fluorouracil-based chemotherapy for patients with HER2-positive metastatic gastric and gastroesophageal junction adenocarcinoma patients: a retrospective study. *Bull Cancer* 2015;102:324–331.
153. Makiyama A, Sukawa Y, Kashiwada T, et al. Randomized, phase II study of trastuzumab beyond progression in patients with HER2-positive advanced gastric or gastroesophageal junction cancer: WJOG7112G (T-ACT Study). *J Clin Oncol* 2020;38:1919–1927.
154. Tabernero J, Ohtsu A, Muro K, et al. Exposure-response analyses of ramucirumab from two randomized, phase III trials of second-line treatment of advanced gastric or gastroesophageal junction cancer. *Mol Cancer Ther* 2017;16:2215–2222.
155. Fuchs CS, Shitara K, Di Bartolomeo M, et al. Ramucirumab with cisplatin and fluoropyrimidine as first-line therapy in patients with metastatic gastric or junctional adenocarcinoma (RAINFALL): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019;20:420–435.
156. U.S. Food and Drug Administration. FDA approves nivolumab in combination with chemotherapy for metastatic gastric cancer and esophageal adenocarcinoma. 2021. Accessed November 4, 2021. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-combination-chemotherapy-metastatic-gastric-cancer-and-esophageal>
157. U.S. Food and Drug Administration. FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. 2017. Accessed February 21, 2020. Available at: <https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm560040.htm>
158. U.S. Food and Drug Administration. FDA approves pembrolizumab for adults and children with TMB-H solid tumors. 2020. Accessed January 19, 2021. Available at: <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adults-and-children-tmb-h-solid-tumors>
159. U.S. Food and Drug Administration. FDA grants accelerated approval to dostarlimab-gxly for dMMR advanced solid tumors. 2021. Accessed August 30, 2021. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dostarlimab-gxly-dmmr-advanced-solid-tumors>
160. Oaknin A, Tinker AV, Gilbert L, et al. Clinical activity and safety of the anti-programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair-deficient endometrial cancer: a nonrandomized phase 1 clinical trial. *JAMA Oncol* 2020;6:1766–1772.
161. Gatalica Z, Xiu J, Swensen J, et al. Molecular characterization of cancers with NTRK gene fusions. *Mod Pathol* 2019;32:147–153.
162. Okamura R, Boichard A, Kato S, et al. Analysis of NTRK alterations in pan-cancer adult and pediatric malignancies: implications for NTRK-targeted therapeutics. *JCO Precis Oncol* 2018;PO.18.00183.
163. Arnold A, Daum S, von Winterfeld M, et al. Analysis of NTRK expression in gastric and esophageal adenocarcinoma (AGE) with pan-TRK immunohistochemistry. *Pathol Res Pract* 2019;215:152662.
164. Shinozaki-Ushiku A, Ishikawa S, Komura D, et al. The first case of gastric carcinoma with NTRK rearrangement: identification of a novel ATP1B-NTRK1 fusion. *Gastric Cancer* 2020;23:944–947.
165. Imbesi JJ, Kurtz RC. A multidisciplinary approach to gastrointestinal bleeding in cancer patients. *J Support Oncol* 2005;3:101–110.
166. Kim YI, Choi IJ. Endoscopic management of tumor bleeding from inoperable gastric cancer. *Clin Endosc* 2015;48:121–127.
167. Sheibani S, Kim JJ, Chen B, et al. Natural history of acute upper GI bleeding due to tumours: short-term success and long-term recurrence with or without endoscopic therapy. *Aliment Pharmacol Ther* 2013;38:144–150.
168. Poultsides GA, Kim CJ, Orlando RIII, et al. Angiographic embolization for gastroduodenal hemorrhage: safety, efficacy, and predictors of outcome. *Arch Surg* 2008;143:457–461.
169. Kim MM, Rana V, Janjan NA, et al. Clinical benefit of palliative radiation therapy in advanced gastric cancer. *Acta Oncol* 2008;47:421–427.
170. Kondoh C, Shitara K, Nomura M, et al. Efficacy of palliative radiotherapy for gastric bleeding in patients with unresectable advanced gastric cancer: a retrospective cohort study. *BMC Palliat Care* 2015;14:37.
171. Jeurnink SM, van Eijck CHJ, Steyerberg EW, et al. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. *BMC Gastroenterol* 2007;7:18–27.
172. Lim S, Muhs BE, Marcus SG, et al. Results following resection for stage IV gastric cancer; are better outcomes observed in selected patient subgroups? *J Surg Oncol* 2007;95:118–122.
173. Holt AP, Patel M, Ahmed MM. Palliation of patients with malignant gastroduodenal obstruction with self-expanding metallic stents: the treatment of choice? *Gastrointest Endosc* 2004;60:1010–1017.
174. Lindsay JO, Andreyev HJN, Vlavianos P, et al. Self-expanding metal stents for the palliation of malignant gastroduodenal obstruction in patients unsuitable for surgical bypass. *Aliment Pharmacol Ther* 2004;19:901–905.
175. Kim TO, Kang DH, Kim GH, et al. Self-expandable metallic stents for palliation of patients with malignant gastric outlet obstruction caused by stomach cancer. *World J Gastroenterol* 2007;13:916–920.
176. Endo S, Takiguchi S, Miyazaki Y, et al. Efficacy of endoscopic gastroduodenal stenting for gastric outlet obstruction due to unresectable advanced gastric cancer: a prospective multicenter study. *J Surg Oncol* 2014;109:208–212.
177. Ly J, O'Grady G, Mittal A, et al. A systematic review of methods to palliate malignant gastric outlet obstruction. *Surg Endosc* 2010;24:290–297.
178. Jeurnink SM, Steyerberg EW, van Hooft JE, et al. Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. *Gastrointest Endosc* 2010;71:490–499.
179. Issaka RB, Shapiro DM, Parikh ND, et al. Palliative venting percutaneous endoscopic gastrostomy tube is safe and effective in patients with malignant obstruction. *Surg Endosc* 2014;28:1668–1673.
180. Wollman B, D'Agostino HB. Percutaneous radiologic and endoscopic gastrostomy: a 3-year institutional analysis of procedure performance. *AJR Am J Roentgenol* 1997;169:1551–1553.
181. Silas AM, Pearce LF, Lestina LS, et al. Percutaneous radiologic gastrostomy versus percutaneous endoscopic gastrostomy: a comparison of indications, complications and outcomes in 370 patients. *Eur J Radiol* 2005;56:84–90.
182. Lee MJ, Saini S, Brink JA, et al. Malignant small bowel obstruction and ascites: not a contraindication to percutaneous gastrostomy. *Clin Radiol* 1991;44:332–334.
183. Ryan JM, Hahn PF, Mueller PR. Performing radiologic gastrostomy or gastrojejunostomy in patients with malignant ascites. *AJR Am J Roentgenol* 1998;171:1003–1006.

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Specialties
Jaffer A. Ajani, MD	Amgen Inc.; Astellas Pharma US, Inc.; Bristol-Myers Squibb Company; Delta Fly Pharma; Gilead Sciences, Inc.; LaNova; Leap; Merck & Co., Inc.; miracogne; NIT; Prolinx; Roche Laboratories, Inc.; Taiho Pharmaceuticals Co., Ltd.; Zymeworks	Amgen Inc.; ARCUS; Astellas Pharma US, Inc.; AstraZeneca Pharmaceuticals LP; BeiGene; Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Daiichi-Sankyo Co.; DAVA/OM; Genes; Gilead Sciences, Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Servier; STEBA; Turning Point; zymeworks	None	Medical Oncology, Gastroenterology
David J. Bentrem, MD, MS	None	None	None	Surgery/Surgical Oncology
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David Cooke, MD	None	None	None	Surgery/Surgical Oncology
Carlos Corvera, MD	None	None	Johnson & Johnson	Radiation Therapy/Radiation Oncology
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Prajan Das, MD, MPH, MS	None	None	None	Radiation Oncology
Peter C. Enzinger, MD	None	ALX Oncology; Arcus Bioscience; Astellas Pharma US, Inc.; AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Daiichi-Sankyo Co.; Five Prime; Ideaya; Istari; Legend; Takeda Pharmaceuticals North America, Inc.; Xencor; Zymeworks	Merck & Co., Inc.	Medical Oncology
Thomas Enzler, MD, PhD	None	None	None	Medical Oncology, Hematology/Hematologic Oncology
Paul Fanta, MD	None	None	None	Medical Oncology, Hematology/Hematologic Oncology
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Michael Gibson, MD, PhD	AbbVie, Inc.; Soligenix	Daiichi-Sankyo Co.; Flagship Biosciences; Merck & Co., Inc.; National Cancer Institute; UpToDate	Bristol-Myers Squibb Company	Hematology/Hematologic Oncology, Medical Oncology, Internal Medicine
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David H. Ilson, MD, PhD	None	Astellas Pharma US, Inc.; AstraZeneca Pharmaceuticals LP; Bayer HealthCare; Bristol-Myers Squibb Company; Eli Lilly and Company; Merck & Co., Inc.; Roche Laboratories, Inc.; Taiho Pharmaceuticals Co., Ltd.	MacroGenics; Merck & Co., Inc.	Internal Medicine, Medical Oncology
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Jill Lacy, MD	None	Aptitude Health; ASCO; Deciphera Pharmaceuticals, Inc.; Ipsen; Novartis Pharmaceuticals Corporation	None	Medical Oncology
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The NCCN Guidelines Staff have no conflicts to disclose.

*The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty: Samuel Klempner, MD: Turning Point Therapeutics; Scott Reznik, MD: Oncano