Abstract: Gastric cancer is not a top-10 malignancy in the United States but represents one of the most common causes of cancer death worldwide. Biological differences between tumors from Eastern and Western countries add to the complexity of identifying standard-of-care therapy based on international trials. Systemic chemotherapy, radiotherapy, surgery, immunotherapy, and targeted therapy all have proven efficacy in gastric adenocarcinoma; therefore, multidisciplinary treatment is paramount to treatment selection. Triplet chemotherapy for resectable gastric cancer is now accepted and could represent a plateau of standard cytotoxic chemotherapy for localized disease. Classification of gastric cancer based on molecular subtypes is providing an opportunity for personalized therapy. Biomarkers, in particular microsatellite instability (MSI), programmed cell death ligand 1 (PD-L1), human epidermal growth factor receptor 2 (HER2), tumor mutation burden, and Epstein-Barr virus, are increasingly driving systemic therapy approaches and allowing for the identification of populations most likely to benefit from immunotherapy and targeted therapy. Significant research opportunities remain for the less differentiated histologic subtypes of gastric adenocarcinoma and those without markers of immunotherapy activity.

Keywords: adenocarcinoma, gastric cancer, immunotherapy, molecular subtypes, stomach neoplasms

Introduction
Although gastric cancer is not in the top 10 malignancies ranked by either incidence or mortality in the United States, it does represent the second most common cause of cancer death worldwide. Therefore, the advances we make in gastric cancer treatment, even in low-incidence countries, can have global implications. Caution must be exercised, however, in applying findings from Eastern countries to Western countries because there are likely differences in biology. Gastric cancers from Eastern countries, such as Japan and Korea, have lower proportions with signet ring histology and proximal stomach involvement. Because of the lower proportion of cases with these adverse factors, most large, randomized trials from the East demonstrate survival rates that are 30% to 40% higher than trials from the West. There are also some basic science studies documenting a difference in tumor biology between regions.

Risk factors for gastric cancer include many nonmodifiable variables, such as age, sex, and race/ethnicity. Other risk factors are controllable, such as infection with Helicobacter pylori bacteria, smoking, and diets high in nitrates and nitrites. There are also several relatively rare risk factors, such as a history of mucosa-associated lymphoid tissue lymphoma, previous stomach surgery, and pernicious anemia. Having a first-degree family member with gastric cancer is also a risk factor. There are several known inherited cancer syndromes that are associated with gastric cancer. The strongest association is found in hereditary diffuse gastric cancer (CDH1) syndrome, in which approximately 80% of patients will develop gastric cancer. Others with a much lower risk include Lynch, hereditary breast and ovarian cancer (BRCA), Li-Fraumeni, familial adenomatous polyposis, and Peutz-Jegher syndromes.
Diagnosis and Staging

Patients with newly diagnosed gastric cancer often present with an upper endoscopy report performed for symptoms, including dyspepsia and reflux, but also with symptoms or signs that may indicate advanced disease, such as dysphagia, weight loss, gastrointestinal bleeding, anemia, and emesis. Clear measurements of the extent of the primary tumor are often lacking, and repeat endoscopy with endoscopic ultrasound can provide additional clinical staging. Endoscopic ultrasound is most beneficial in identifying the rare early tumor (T1; AJCC), which may benefit from endoscopic resection or upfront surgery. Most tumors are T2 through T4, however, and there are known limitations in the ability of endoscopic ultrasound and imaging to accurately identify nodal metastases. Standard chest/abdomen/pelvic computed tomography (CT) scans are often sufficient for imaging, but fludeoxyglucose–positron emission tomography (FDG-PET)/CT scans can be considered for specific clinical indications, such as further evaluation of indeterminate lesions. Tumors with poorly differentiated signet ring cell type histology or those without mucinous features often do not demonstrate increased uptake on PET-CT imaging.

Staging laparoscopy with peritoneal washings is a critical component of the initial workup, as carcinomatosis is identified in approximately 20% of patients without imaging evidence of peritoneal disease. In addition, positive peritoneal cytology only is identified in another approximately 10% of patients, which also represents stage IV disease. Although only assigned a category 2B recommendation in current National Comprehensive Cancer Network (NCCN) guidelines (which indicates there is not uniform NCCN consensus that the procedure is appropriate, as it would be in a 2A recommendation), the procedure is considered standard at many cancer centers because of the obvious implications of identifying stage IV radiologically occult disease at diagnosis. The risks of staging laparoscopy are low, and the outpatient procedure can also be combined with port placement for prompt initiation of systemic therapy. If the staging laparoscopy is deferred until the time of attempted resection after preoperative therapy, the identification of stage IV disease represents progression of disease when it was possibly present at the time of diagnosis. Appropriate initial staging at diagnosis has clear systemic therapy implications, can prevent unnecessary delays while awaiting surgery, and can also promote access to clinical trials. Most importantly, however, is that patients deserve a clear understanding of the extent of their disease and potential for cure as early as possible in their treatment plan.

A relatively new development in the workup of patients with potentially resectable disease is consideration of microsatellite instability (MSI) testing at diagnosis. There are several studies providing a signal that patients with MSI-high cancers may have an adverse oncologic outcome when treated with standard systemic chemotherapy approaches. In a secondary post hoc analysis of the MAGIC trial (International Standard Randomized Controlled Trial Number [ISRCTN] 93793971), compared with patients who had microsatellite-stable/MSI-low tumors, those who had MSI-high tumors had improved survival with surgery alone and inferior survival with perioperative chemotherapy plus surgery. Similarly, a post hoc analysis of the CLASSIC trial (ClinicalTrials.gov identifier NCT00411229) showed that patients with resected MSI-high tumors did not have a disease-free survival (DFS) benefit with adjuvant chemotherapy. In a pooled meta-analysis of 4 randomized controlled trials of resected gastric cancer, MSI-high status was associated with longer overall survival (OS) and lack of benefit with perioperative or adjuvant chemotherapy. Some centers are recommending upfront surgery for patients with MSI-high tumors and even consideration of preoperative immunotherapy for advanced locoregional disease. The role of perioperative immune checkpoint blockade or omission of chemotherapy in operable MSI-H tumors has not been prospectively assessed. KEYNOTE-585 is a phase 3, randomized, double-blind study assessing the addition of pembrolizumab to perioperative chemotherapy in resectable gastroesophageal cancers (ClinicalTrials.gov identifier NCT03221426), and this may provide data on the role of checkpoint blockade in the subset of patients with MSI-H cancers. These complex cases are best approached in a multidisciplinary fashion with input from medical, radiation, and surgical oncology.

National guidelines recommend a multidisciplinary team approach to therapeutic decisions for patients with gastric cancer. Meetings are encouraged at least once a week with individuals from relevant disciplines to include gastroenterology, radiology, pathology, and medical, surgical, and radiation oncology. A review of pathology and imaging is often helpful and not infrequently identifies findings that can change treatment or require further workup. In addition, a review of patient outcomes and novel studies can provide an excellent source of continued medical education.

Management—Localized Disease

Randomized clinical trials provide evidence that combined modality therapy is effective for patients with nonmetastatic gastric and gastroesophageal adenocarcinoma. Perioperative chemotherapy or postoperative chemotherapy plus chemoradiation are listed as preferred approaches in current guidelines, although postoperative chemotherapy is also an option after an adequate lymph node dissection. Studies of large databases, such as the
National Cancer Database, demonstrate an increase in the application of neoadjuvant therapy, but it appears that from one-third to one-fourth of patients still undergo a surgery-upfront approach.22

Perioperative Chemotherapy
For potentially resectable patients with clinical T2N0 or greater disease, neoadjuvant/peroperative therapy is typically administered rather than upfront surgery followed by adjuvant therapy. Although there are no randomized trials comparing these approaches, the former approach has a greater likelihood of maximum systemic therapy delivery. Neoadjuvant chemotherapy may also result in downstaging of a locally advanced tumor, address micrometastatic disease, and improve the identification of patients for whom surgery may not offer a survival benefit because of disease progression during neoadjuvant therapy.

The MAGIC trial was a seminal study that established the survival benefit of perioperative chemotherapy plus surgery versus surgery alone in patients with operable gastroesophageal adenocarcinoma (5-year survival, 36% vs 23%).23 Perioperative chemotherapy consisted of a 3-drug combination of epirubicin, cisplatin, and fluorouracil (ECF). The anthracycline epirubicin is now thought to add additional toxicity without benefit and no longer is used in modern perioperative regimens.24 In support of this conclusion is a phase 3 trial that compared surgery with or without perioperative regimens.24 In support of this conclusion is a similar 5-year OS benefit of 38% versus 24% in favor of perioperative chemotherapy.25

Most recently, the phase 2/3 FLOT4-AIO trial (ClinicalTrials.gov identifier NCT01216644) compared perioperative FLOT (fluorouracil plus leucovorin, oxaliplatin, and docetaxel) with ECF (or ECX, where X refers to capecitabine) in patients with resectable gastroesophageal adenocarcinoma. Perioperative FLOT resulted in superior OS compared with ECF/ECX (median OS, 50 vs 35 months).26 Notably, patients in the FLOT arm had a 9% improvement in 5-year OS rates (45% vs 36%). Although there are concerns over the comparative arm that includes epirubicin, which has doubtful efficacy in gastric cancer, FLOT is a new standard of care. In less fit patients, we prefer perioperative therapy with a fluoropyrimidine plus platinum doublet.

The roles of human epidermal growth factor 2 (HER2)-targeted agents and vascular endothelial growth factor (VEGF) inhibition are established in the metastatic setting and are currently being explored in the perioperative setting using a FLOT backbone. In the randomized phase 2 PETRARCA trial (ClinicalTrials.gov identifier NCT02581462), the addition to trastuzumab and pertuzumab to perioperative FLOT improved the pathologic complete response rate (35% vs 12%) and the nodal negativity rate (68% vs 39%) in patients with HER2-positive, resectable gastroesophageal adenocarcinoma. Despite the negative results of the JACOB trial (ClinicalTrials.gov identifier NCT01774786), these striking results warrant further investigation of perioperative trastuzumab plus pertuzumab in the phase 3 setting.27 In the randomized phase 2 portion of the RAMSES/FLOT7 trial (ClinicalTrials.gov identifier NCT02661971), the addition of ramucirumab to FLOT improved R0 (no residual cancer) resection rates (97% vs 83%) but did not impact pathologic response.28

Adjuvant Chemotherapy
In patients with gastric cancer who undergo upfront surgery and have pathologic T3 or T4 lesions or lymph node-positive disease, adjuvant therapy is recommended. The CLASSIC trial established the benefit of adjuvant capecitabine and oxaliplatin in patients who undergo curative-intent gastrectomy with D2 (extended) lymph node dissection.29 Because this trial was performed in South Korea, China, and Taiwan, the previously mentioned issues regarding biologic differences between East Asia and US/European gastric cancers apply. The 3-year DFS rate was 74% in the adjuvant chemotherapy group versus 59% in the surgery only group. In countries where the oral fluoropyrimidine S-1 is approved, adjuvant S-1 monotherapy or S-1 plus docetaxel can also be considered. In the randomized phase 3 ACTS-GC trial (ClinicalTrials.gov identifier NCT00152217), adjuvant S-1 for 1 year demonstrated a survival benefit compared with surgery alone (5-year OS, 72% vs 61%).30 In the phase 3 JACCRO GC-07 trial (University Hospital Identification Network [UMIN] identifier R00012099), patients with pathologic stage 3 gastric cancer who underwent curative-intent surgery with D2 lymphadenectomy were randomized to receive either S-1 plus docetaxel or S1 alone.31 At interim analysis, 3-year recurrence-free survival was better in the combination group (66% vs 50%).

Adjuvant Chemoradiotherapy
The role of adjuvant radiotherapy is less certain. The Intergroup 0116 (INT 0116) trial showed a 9-month OS benefit in favor of adjuvant chemoradiation versus observation in patients with gastroesophageal adenocarcinoma who underwent curative-intent surgery.32 However, that study was limited by the finding that only 10% of patients underwent D2 lymphadenectomy. Therefore, adjuvant chemoradiation may have compensated for an inadequate surgery, and it was questioned whether this benefit would actually persist if appropriate D2 lymphadenectomy had been performed. Subsequent trials that compared adjuvant chemotherapy with or without adjuvant chemoradiotherapy have produced conflicting results.33-35 According to the NCCN guidelines, adjuvant chemoradiation can be given for patients after R1...
(microscopic residual cancer) or R2 (macroscopic residual cancer) resection. It also represents a category 1 recommendation as part of adjuvant therapy in patients with pathologic T3 and T4 (pT3-pT4) or pathologic lymph node (pN-positive) disease if less than D2 nodal dissection is performed. Studies using the National Cancer Database demonstrate an increasing use of perioperative chemotherapy with a decreasing use of postoperative chemoradiotherapy, likely because of improved tolerance for preoperative approaches, concerns over toxicity with postoperative chemoradiotherapy, and the increasingly recognized importance of D2 lymph node dissection.

Preoperative Chemoradiotherapy
Preoperative chemoradiation is a category 2B (based on lower-level evidence) treatment option for patients undergoing a preoperative therapy or total neoadjuvant treatment approach. Regimens included in current guidelines are based on phase 3 randomized controlled trials including gastroesophageal junction tumors or smaller nonrandomized phase 2 studies.

Endoscopic Resection
Thin, early stage gastric cancers are infrequently detected in Western populations to allow for endoscopic resection. The criteria for safe and appropriate endoscopic resection are extensive: well to moderately differentiated tumor histology, size ≤2 cm, without invasion of the deep submucosa, and without lymphovascular invasion. Of critical importance, clear negative lateral and deep margins must be obtained. Because these lesions are rare within the US population, it is often difficult for endoscopic practitioners to obtain and maintain proficiency in advanced techniques such as endoscopic mucosal or submucosal resection.

Surgical Resection
Surgical options for gastric cancer are primarily subtotal or total gastrectomy. There are several reasons to exercise caution in considering nonanatomic wedge-type resections or limited proximal gastrectomy. First, approximately 75% of tumors in Western populations are poorly differentiated and thus spread in a diffuse fashion that requires wide resection to ensure negative margins. Second, lymph node involvement is found in approximately 10%, 34%, and 44% of T1a, T1b, and T2 tumors, respectively. Third, proximal gastrectomy with resection of the vagus nerve branches may predispose patients to severe chronic reflux. Finally, ensuring an adequate D2 lymph node dissection requires anatomic resection, and it is unclear whether more limited resections adversely impact cancer outcomes.

Although technical aspects can vary among various approaches, the following steps will help illustrate the
anatomical details of gastrectomy. The greater omentum is separated from the transverse mesocolon, as demonstrated in Figure 1. The right gastroepiploic and gastric vessels and duodenum are transected (Fig. 2). Then, the left gastric vessels are cut (Fig. 3) before transection of the stomach for subtotal gastrectomy (Fig. 4). Reconstruction for subtotal gastrectomy is illustrated in Figure 5. For tumors extending more proximally, the short gastric vessels are also transected, and reconstruction is performed similar to the illustration in Figure 6.

The extent of D1, or regional, lymphadenectomy is shown in Figure 7. Extended, or D2, lymphadenectomy is essentially the removal of lymph nodes along the branches of the celiac trunk, as shown in Figures 8 and 9. A Japanese gastric cancer staging system exists that classifies individual areas of lymph nodes according to a numerical system, as partly illustrated in Figures 8 and 9.43

Treatment of Metastatic and Unresectable Gastric Cancer
Several cytotoxic agents are active in advanced gastric cancer, including fluoropyrimidines, platinums, taxanes, and irinotecan. The choice of treatment depends on patient performance status and medical comorbidities as well as the toxicity profile of the regimen. Combination regimens offer higher response rates and improved survival compared with single-agent therapy. Treatment goals are typically palliative in intent and are aimed at controlling symptoms, controlling disease, and extending life. Although there is no universal standard first-line therapy, a fluoropyrimidine and platinum doublet is typically the preferred backbone regimen for most patients. Oxaliplatin is considered to be as effective as cisplatin and is the choice platinum in most modern regimens.44 In very fit patients who are willing to sacrifice toxicity for higher response rates and potentially longer PFS, a triplet regimen combining a fluoropyrimidine, oxaliplatin, and docetaxel can be considered.45 There is no role for epirubicin in contemporary regimens for advanced disease.46 In patients who are not candidates for intensive therapy, single-agent therapy with a fluoropyrimidine, irinotecan, or taxane can be considered. In patients with overexpression or amplification of HER2 (also known as ERBB2), trastuzumab should be added to cytotoxic first-line chemotherapy, as reviewed in detail below. In patients with a programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥5, nivolumab should be added to first-line chemotherapy, as also discussed below. In the second-line treatment for metastatic gastric cancer, cytotoxic chemotherapy agents not already used in the first line can be attempted. Several years ago, ramucirumab
was added to the armamentarium of active agents in this disease. Ramucirumab is a monoclonal antibody that binds to VEGF receptor-2 (VEGFR-2), blocking receptor activation. In the phase 3 REGARD trial (ClinicalTrials.gov identifier NCT00917384), ramucirumab was shown to have a 1.4-month survival benefit compared with placebo in the second-line treatment of advanced gastric adenocarcinoma.47 Subsequently, the phase 3 RAINBOW trial (ClinicalTrials.gov identifier NCT01170663) demonstrated that paclitaxel plus ramucirumab was superior to paclitaxel plus placebo in the second-line setting with an OS of 9.6 versus 7.4 months.48 In fit patients, paclitaxel plus ramucirumab is a preferred second-line regimen after progression on a fluoropyrimidine and platinum doublet. Otherwise, single-agent cytotoxic chemotherapy or ramucirumab monotherapy can be considered. The oral cytotoxic agent trifluridine-tipiracil, combining an antimetabolite trifluridine with a thymidine phosphorylase inhibitor (tipiracil), has been shown in the phase 3 setting to have a survival benefit over placebo (5.7 vs 3.6 months) in treatment-refractory gastric cancer and is now an approved third-line regimen.49 The role of immunotherapy and targeted therapies in gastric cancer is discussed further below, with an emphasis on recent progress and biomarkers, including MSI high (MSI-H), PD-L1, tumor mutation burden (TMB), Epstein-Barr virus (EBV), and HER2.

Immunotherapy in Gastric Cancer

In the last decade, immune checkpoint blockade has emerged as an exciting treatment strategy across a spectrum of malignancies. This includes monoclonal antibodies that inhibit programmed cell death protein 1 (PD-1), PD-L1, and cytotoxic T-lymphocyte antigen 4 (CTLA-4).

High Microsatellite Instability/Mismatch Repair-Deficient Tumors

The Cancer Genome Atlas (TCGA) Research Network performed a comprehensive molecular characterization of 295 untreated gastric adenocarcinomas and categorized gastric cancer into 4 subtypes: MSI-H tumors, EBV-positive tumors, tumors exhibiting chromosomal instability (CIN), and genomically stable tumors.50 In that analysis of untreated tumors, 22% were MSI-H; however, the reported incidence in metastatic disease was much lower at only 3% in a recent cohort of patients with stage IV disease.51 Mismatch repair (MMR) genes are responsible for fixing errors that occur during deoxyribonucleic acid (DNA) replication. Tumors with defects in the mismatch repair system (MMR-deficient [dMMR]) harbor significantly more mutations than tumors with intact MMR machinery (MMR-proficient). dMMR tumors are vulnerable to mutations in microsatellites, which are repetitive sequences of nucleotide bases found throughout the genome, leading to high levels of MSI. Across tumor types, patients with dMMR cancers are more likely to respond to PD-1 blockade than those with MMR-proficient cancers.52 In part, this is because of high levels of neoantigens and PD-L1-positive T-cell infiltration in dMMR tumors.

Pembrolizumab is a humanized monoclonal antibody that inhibits PD-1 activity by binding to PD-1 receptors on T cells, thereby blocking PD-1 ligands (PD-L1 and
PD-L2) from binding. PD-1 blockade results in removal of the physiologic brake on an active immune system and induces antitumor response. KEYNOTE-158 (ClinicalTrials.gov identifier NCT02628067) was a phase 2 trial that enrolled patients with treatment-refractory, noncolorectal MSI-H/dMMR cancers to receive pembrolizumab. Of the 24 patients with gastric cancer, there were 11 responses (including 4 complete responses), and the median PFS was 11 months. This trial ultimately led to the tissue-agnostic US Food and Drug Administration (FDA) approval of pembrolizumab for patients with unresectable or metastatic MSI-H or dMMR tumors of any solid tumor type, including gastric cancer, who progressed after prior treatment and have no satisfactory alternative treatment.

Prospective tumor sequencing of patients with metastatic gastroesophageal adenocarcinoma has demonstrated that patients with MSI-H tumors are chemotherapy-resistant and more likely to obtain durable responses to immunotherapy. An analysis of patients with MSI-H gastric cancers enrolled on the KEYNOTE-059 (ClinicalTrials.gov identifier NCT02335411), KEYNOTE-061 (ClinicalTrials.gov identifier NCT02370498), and KEYNOTE-062 (ClinicalTrials.gov identifier NCT02494583) trials indicated that both OS and PFS were prolonged in those who received pembrolizumab monotherapy compared with those who received chemotherapy and that pembrolizumab was more effective than chemotherapy in the first-line setting.

Immunotherapy Trials in Gastric Adenocarcinoma

KEYNOTE-059 was a phase 2 trial of pembrolizumab therapy in patients with advanced gastric cancer who had disease progression after ≥2 lines of therapy. Overall, the objective response rate (ORR) was 11.6%, and the median duration of response (DoR) was 8.4 months. However, in PD-L1–positive (CPS ≥1) patients, the ORR was 15.5%, and the median DoR was 16.3 months. These results were the basis of the FDA approval of pembrolizumab for third-line treatment of PD-L1–positive (CPS ≥1) gastric adenocarcinoma.

Pembrolizumab was compared with paclitaxel in the second-line treatment of advanced gastric adenocarcinoma in the randomized phase 3 KEYNOTE-061 trial. In an updated analysis, pembrolizumab did not significantly improve survival compared with paclitaxel in the second-line setting. However, pembrolizumab numerically prolonged OS and showed increasing benefit with higher PD-L1 scores, with fewer treatment-related adverse events.

KEYNOTE-062 was a phase 3 trial comparing pembrolizumab with or without chemotherapy versus chemotherapy for first-line treatment of PD-L1–positive (CPS ≥1) gastric or gastroesophageal junction adenocarcinoma. Compared with chemotherapy, pembrolizumab was noninferior for OS in patients who had a CPS ≥1. In those who had a CPS ≥10, pembrolizumab improved OS compared with chemotherapy; however, this difference was not statistically tested.
Pembrolizumab plus chemotherapy did not improve OS or PFS in patients who had CPS ≥1 or ≥10.

Nivolumab is another humanized monoclonal antibody that inhibits PD-1. In the phase 3 ATTRACTION-2 trial (ClinicalTrials.gov identifier NCT02267343), there was a survival benefit of nivolumab compared with placebo in heavily pretreated patients with advanced gastric adenocarcinoma (5.3 vs 4.1 months). This study was performed in an Asian population and did not select for PD-L1 expression. Nivolumab is now approved in Japan for advanced gastric cancer refractory to conventional chemotherapy, regardless of PD-L1 expression. Nivolumab alone and in combination with ipilimumab (a monoclonal antibody inhibiting CTLA-4) has been studied in Western populations with chemotherapy-refractory gastroesophageal adenocarcinoma and has been shown to have encouraging antitumor activity with an acceptable toxicity profile. CheckMate-649 (ClinicalTrials.gov identifier NCT02872116) is a phase 3 trial investigating nivolumab plus chemotherapy or nivolumab plus ipilimumab versus chemotherapy alone in the first-line treatment of metastatic, HER2-negative gastric cancer. In initial results, patients with PD-L1 CPS ≥5 receiving nivolumab plus chemotherapy compared with chemotherapy alone had improved OS (14.4 vs 11.1 months) at a prespecified interim analysis and improved PFS (7.7 vs 6.1 months) at final analysis. An OS benefit was also seen in the all-randomized population. This is a practice-changing study that establishes chemotherapy plus nivolumab as a new standard of care for first-line treatment of HER2-negative gastric cancer in patients with PD-L1 CPS ≥5. However, this regimen is not yet FDA approved nor is it known what CPS cutoff will be used.

Unfortunately, a survival benefit was not shown for the PD-L1 inhibitor avelumab compared with clinicians’ choice therapy in the third-line setting.
Tumor Mutation Burden

Gastric cancer is a heterogeneous group of diseases with variable responsiveness to immunotherapy. Many biomarkers have been examined to identify susceptibility to PD-1 blockade, including MSI status and PD-L1 expression, as discussed earlier. TMB is another biomarker currently under investigation. TMB quantifies the number of somatic mutations per coding area of a genome. It has been hypothesized that a heavily mutated tumor can produce a large number of neoantigens, resulting in T-cell infiltration and potentially increased responsiveness to checkpoint blockade.

In June 2020, the FDA granted accelerated approval for the treatment of patients with unresectable or metastatic TMB-high (TMB-H) (≥10 mutations per megabase) solid tumors that progressed after prior treatment and had no satisfactory alternative treatment options. This was based upon a prospectively planned retrospective analysis of previously treated patients with advanced solid tumors and TMB-H enrolled on KEYNOTE-158. In this nonrandomized trial, of 790 evaluable patients, 102 (13%) were had TMB-H status and an ORR of 29%, with a median DoR not reached. In an exploratory analysis from KEYNOTE-061, there was a positive association between TMB determined by FoundationOne CDx analysis (Foundation Medicine) and clinical outcomes in patients with gastric cancer treated with pembrolizumab, but not paclitaxel. In patients with TMB ≥10 mutations per megabase, pembrolizumab demonstrated an OS benefit compared with paclitaxel, and this benefit persisted even when patients who had MSI-H tumors were excluded. These findings are hypothesis-generating. In contrast, a retrospective analysis of genomically profiled gastro-esophageal adenocarcinomas found that, although survival was associated with increasing TMB, this association was lost after multivariate analysis and exclusion of patients who had MSI-H tumors.

Epstein-Barr Virus

EBV is a human herpes virus implicated in several malignancies, including gastric adenocarcinoma. EBV-positive gastric cancer is a distinct subset of gastric cancer identified by TCGA and is associated with a rich CD8-positive...
T-cell infiltrate and increased PD-L1 and PD-L2 expression, which may potentially make it more susceptible to PD-1 blockade. Several reports have described robust responses of EBV-positive tumors to immune checkpoint blockade; however, this needs to be prospectively studied.

HER2-Positive Gastric Cancer

Approximately 15% to 20% of advanced gastric and gastroesophageal junction adenocarcinomas have overexpression or amplification of HER2. HER2 positivity is more commonly seen in intestinal-type cancers compared with diffuse-type or mixed-type cancers, in the TCGA CIN subtype, and in cancers arising from the gastroesophageal junction compared with those arising in the body of the stomach.

Trastuzumab is a humanized monoclonal antibody that targets the HER2 receptor, inhibits downstream signal activation, and induces antibody-dependent cellular toxicity. The pivotal phase 3 ToGA trial (ClinicalTrials.gov identifier NCT01041404) established the addition of trastuzumab to chemotherapy as the standard of care in the first-line treatment of advanced HER2-positive gastric adenocarcinoma. Trastuzumab plus chemotherapy improved median OS compared with chemotherapy alone, particularly in a post-hoc analysis of patients who had HER2 immunohistochemistry scores of 3+ or HER2 immunohistochemistry scores of 2+ with fluorescent in situ hybridization-positive tumors (16.0 vs 11.8 months). The level of ERRB2 amplification quantified by next-generation sequencing is correlated with PFS on trastuzumab, with higher ERRB2 amplification levels associated with longer PFS on first-line trastuzumab. Conversely, co-occurring alterations in the RTK-RAS-PI3K pathway are associated with a shorter time to progression on first-line trastuzumab–based therapy.

Various subsequent attempts to target HER2 have been disappointing. Lapatinib, a tyrosine kinase inhibitor affecting both HER2 and epidermal growth factor receptor (EGFR), does not improve survival when combined with chemotherapy in both first-line and second-line settings in metastatic HER2-positive gastric adenocarcinoma. Trastuzumab emtansine, an antibody-drug conjugate of trastuzumab bound to the tubulin inhibitor emtansine, does not prolong OS in the second-line treatment of HER2-positive patients. Pertuzumab, a humanized monoclonal antibody that binds to a different epitope on the HER2 receptor, in addition to trastuzumab and chemotherapy, also failed to show a survival benefit in the first-line JACOB trial (ClinicalTrials.gov identifier NCT01774786). Finally, trastuzumab beyond progression has not been shown to improve survival. In patients who progressed on first-line trastuzumab plus chemotherapy, trastuzumab plus paclitaxel did not improve PFS.
compared with paclitaxel alone. However, that trial only mandated HER2 positivity before first-line therapy, and reconfirmation of HER2-positive status before continuing trastuzumab was not required. Exploratory analysis revealed that HER2 positivity was lost after first-line chemotherapy in 11 of 16 evaluable patients. Given the potential for loss of HER2 expression over time, second-line trials targeting HER2 should require re-demonstration of HER2 positivity. There is enthusiasm surrounding several novel HER2-targeted agents. ZW25 has been shown to be well tolerated with single-agent activity in a heavily pretreated group of HER2-positive malignancies. Margetuximab has also demonstrated tolerability and antitumor activity in HER2-positive cancers. Most promising at this point in time is trastuzumab deruxtecan, a humanized monoclonal anti-HER2 antibody attached to a cytotoxic topoisomerase I inhibitor through a cleavable linker. DESTINY-Gastric01 (ClinicalTrials.gov identifier NCT03329690) was a randomized phase 2 trial that evaluated trastuzumab deruxtecan versus chemotherapy in a refractory population of patients with HER2-positive gastric and gastroesophageal adenocarcinoma who had progressed on ≥2 prior therapies, including trastuzumab. Trastuzumab deruxtecan showed improvements in OS (12.5 vs 8.4 months) and the response rate (RR) (51% vs 14%) compared with chemotherapy. Side effects were notable for myelosuppression and interstitial lung disease.

Immunotherapy has also been successfully added to HER2-directed therapy. A phase 2 trial demonstrated that pembrolizumab could be safely combined with trastuzumab plus chemotherapy in HER2-positive, metastatic gastroesophageal adenocarcinoma. Notably, there was an impressive 91% RR and a median OS of 27.3 months, which were much higher than what was seen with chemotherapy plus trastuzumab (RR, 47%), suggesting that there may be a synergistic benefit of combining checkpoint blockade with standard trastuzumab plus chemotherapy. Efficacy is currently being evaluated in the randomized, double-blind phase 3 KEYNOTE-811 trial (ClinicalTrials.gov identifier NCT03615326).

**Antiangiogenic Therapy**

As discussed above, ramucirumab, a monoclonal antibody against VEGFR-2, has a proven survival benefit in the second-line treatment of gastric cancer, both as monotherapy and in combination with paclitaxel. Lenvatinib and regorafenib, both multikinase inhibitors of angiogenic (including VEGF receptor) and oncogenic receptor tyrosine kinases, have been investigated in combination with immunotherapy in East Asian populations. Lenvatinib has been safely combined with pembrolizumab, with a 69% RR in the first-line and second-line treatment of advanced gastric cancer. The addition of regorafenib to nivolumab has also been shown to be safe, with encouraging antitumor activity in the phase 1 setting. We look forward to exploring the efficacy of combined VEGF inhibition and PD-1 blockade in larger cohorts of patients.
Investigational Biomarkers and Future Therapies

Targeting EGFR is a therapeutic strategy in development in gastric cancer. Although EGFR inhibitors are active in several cancers, these drugs have not shown efficacy in the phase 3 setting in unselected patients. In REAL-3 (first-line chemotherapy with or without panitumumab; ClinicalTrials.gov identifier NCT00824785), EXPAND (first-line chemotherapy with or without cetuximab; ClinicalTrials.gov identifier NCT00678535), and the COG trial (second-line gefitinib vs placebo; ISRCTN 29580179), EGFR inhibition failed to improve survival.81-83 In a prospective cohort, patients with metastatic gastroesophageal adenocarcinoma were screened for EGFR amplification, and 8 of 140 (6%) were identified, of whom 7 patients received anti-EGFR therapy.84 The ORR was 58% (4 of 7 patients), and the disease control rate was 100% (7 of 7 patients), suggesting that EGFR inhibition should be further studied in selected patients.

Claudin 18.2, a protein expressed by a subset of gastric cancers, is a novel target for drug development. Zolbetuximab, a chimeric monoclonal antibody that binds to Claudin 18.2, is tolerable, with antitumor activity both as monotherapy and in combination with chemotherapy in patients with Claudin 18.2-positive gastroesophageal adenocarcinoma, and is being further investigated in the phase 3 setting.85,86

In addition to drug development aimed at targeting specific biomarkers, systemic therapy can also be guided and informed by advanced imaging techniques. One of the challenges of biomarker-driven therapy is intratumoral heterogeneity, which can lead to varying responsiveness to targeted therapies. PET using novel tracers, such as radiolabeled trastuzumab, may help assess and monitor tumor heterogeneity over time and is an area of active investigation.87

Recent Progress in Surgery

Because the peritoneum is the most common site of metastatic disease at diagnosis but also the most common site of recurrence after potentially curative surgery, it is a good target for novel therapeutic approaches.16,88 Existing systemic chemotherapy has been shown to improve survival for peritoneal disease, but only at a median of 4 months according to population-based studies.89 There has been some enthusiasm for applying heated intraperitoneal chemotherapy (HIPEC) in patients with gastric cancer based on the improved survival in peritoneal disease from other primary sites, such as appendiceal mucinous tumors, ovarian cancer, and mesothelioma. There is only one completed and published randomized controlled trial of HIPEC in gastric cancer patients with peritoneal disease.90 This small study, from China, demonstrated improved survival for patients undergoing cytoreduction and HIPEC compared with those who underwent cytoreduction alone. However, the survival rates were modest, and not all patients received systemic therapy before surgery in the trial. A recent multi-institutional registry report from Europe also compared patients undergoing cytoreduction versus those undergoing cytoreduction and HIPEC.91 Notably, the patients
who underwent HIPEC demonstrated a long-term survival rate of 20%. A prospective, randomized controlled trial with a similar design to investigate the benefits of HIPEC in addition to cytoreduction, the GASTRIPEC trial (ClinicalTrials.gov identifier NCT02158988), was closed early but should provide randomized controlled data regarding HIPEC.92 Another study from Europe, the PERISCOPE II trial (ClinicalTrials.gov identifier NCT03348150), will answer perhaps the most important question in comparing standard-of-care systemic chemotherapy with HIPEC.93

An older body of literature exists regarding HIPEC in patients with gastric cancers at high risk of developing peritoneal disease, such as T3 and T4 category lesions, albeit exclusively from Chinese and Japanese centers.94 These studies are dated, and adjuvant HIPEC is not a standard of care in Eastern or Western centers. Most studies of peritoneal disease in Japan currently focus on the efficacy of intraperitoneal in combination with systemic paclitaxel.95 However, the role of adjuvant HIPEC in Western populations is an active question and should be answered by the ongoing GASTRICHIP randomized controlled trial (ClinicalTrials.gov identifier NCT01882933).96

### Novel Approaches to Detect Recurrence and Future Directions

Despite the advances made in the multimodality treatment of gastric cancer, recurrences are common. Current research is aimed at identifying patients at risk for recurrence after definitive therapy, with the hope of intervening and potentially improving outcomes. In patients with cancer, circulating tumor DNA (ctDNA) can be detected in the bloodstream and can be a marker of minimal residual disease if detected after definitive therapy. A liquid biopsy can capture the spectrum of alterations present in a heterogeneous tumor compared with a traditional tissue biopsy. However, this DNA needs to be distinguished from cell-free DNA alterations that exist from clonal hemopoiesis. Recently reported was an analysis of samples from patients in the CRITICS trial (ClinicalTrials.gov identifier NCT02931890), a study that investigated perioperative therapies in patients with resectable gastric cancer. ctDNA was identified after filtering alterations from matched white blood cells and predicted recurrence after treatment.97 In another 1630-patient cohort of ctDNA results, genomic alterations were correlated with clinicopathologic characteristics and outcomes and provided prognostic and predictive information.98 Future research should be aimed at prospectively collecting ctDNA to confirm these findings. The presence of persistent ctDNA after curative-intent treatment of gastric cancer may be a marker of minimal residual disease, and trials are currently underway to determine whether additional adjuvant therapy can result in clearance of ctDNA. Specifically, adjuvant pembrolizumab is being investigated in MSI-tumors (ClinicalTrials.gov identifier NCT03832569), and adjuvant trastuzumab plus pembrolizumab versus trastuzumab is being studied in HER2-positive tumors (ClinicalTrials.gov identifier NCT04510285).

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