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Biologic therapy in esophageal and gastric malignancies: current therapies and future directions

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Abstract: Biologic agents, including targeted antibodies as well as immunomodulators, are demonstrating unparalleled development and study across the entire spectrum of human malignancy. This review summarizes the current state of biologic therapies for esophageal, esophagogastric, and gastric malignancies, including those that target human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), c-Met, mechanistic target of rapamycin (mTOR) and immunomodulators. We focus primarily on agents that have been included in phase II and III clinical trials in locally advanced, progressive, or metastatic esophageal and gastric malignancies. At this time, only two biologic therapies are recommended by the National Comprehensive Cancer Network (NCCN): trastuzumab for patients with esophageal/esophagogastric or gastric adenocarcinomas with HER2 overexpression and ramucirumab, a VEGFR-2 inhibitor, as a second-line therapy for metastatic disease. However, recent reports of increases in overall and progression-free survival for agents including pertuzumab, apatinib, and pembrolizumab will likely increase the use of targeted biologic therapy in clinical practice for esophageal and gastric malignancies.

Keywords: Esophageal cancer; gastric cancer; biologic therapy; immunomodulator therapy

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Introduction

Esophageal and gastric cancers continue to pose a significant burden of morbidity and mortality globally. In 2012, it was estimated that gastric cancer was the fifth most common cancer worldwide, and the third leading cause of cancer death (1). Esophageal cancer, while incidentally less common than gastric cancer, has a striking mortality rate, placing it as the sixth leading cause of cancer related deaths worldwide (1). Furthermore, it has been known for the past few decades that the incidence of esophageal adenocarcinoma has substantially increased, mirroring the prevalence of gastroesophageal reflux disease and Barrett's esophagus, particularly in North American and Europe (2,3).

While important advances have been made in the early detection and treatment of esophageal and gastric cancers, the majority of patients continue to present with clinical evidence of regional or distant disease (4). While treatment for esophageal and gastric cancers has traditionally involved combinations of aggressive surgical resection, chemotherapy, and radiotherapy, the percent of patients achieving 5-year survival remains under 20% (4). Because of the intractable nature of these diseases, it is not surprising that attention has turned towards biologic therapies to offer a more tailored, and potentially effective, treatment option. This review will examine biologic therapies that now have established efficacy in esophageal and gastric cancers, as well as those that are currently under investigation and hold

Table 1 Potential biologic targets in esophageal, esophagogastric, and gastric malignancies, and the agents that have been evaluated to date

Biologic target	Targeted agents evaluated for esophageal, EGJ, and gastric malignancies
HER-2	Trastuzumab approved in 1 st -line; Negative studies with lapatinib and T-DM1 (trastuzumab emtansine) in 2 nd -line; Pertuzumab remains under investigation (JACOB trial, TRAP trial)
EGFR	Multiple negative studies with cetuximab and panitumumab in a variety of clinical settings
VEGF and VEGFR	Ramucirumab approved in 2 nd -line; Negative 1 st -line studies with ramucirumab, ziv-aflibercept and bevacizumab; Positive phase III study of apatinib in the refractory setting
c-MET	Negative 1 st -line studies with foretinib, onartuzumab, and rilotumumab
mTOR	Negative 2 nd -line study with everolimus
PD-1	Pembrolizumab and nivolumab with promising phase I/II trials, need to be evaluated with phase III study

potential benefit (*Table 1*).

Human epidermal growth factor receptor 2 (HER2) targeted therapies

Initially discovered as an overexpressed transmembrane tyrosine kinase receptor in approximately one-third of breast cancer patients that was associated with decreased survival, HER2, or c-erb-2, proto-oncogene quickly became an important tumor marker and target for therapy (5). Given the fact that HER2 is constitutively expressed on many different epithelial cell types, studies sought to understand its prevalence in other malignancies, including esophageal and gastric cancers (6). It is estimated that approximately 30% of gastroesophageal adenocarcinomas and 20% of gastric cancers overexpress HER2, and early studies showed wide variability of overexpression depending on the specific method of testing (7,8). Rates for HER2 overexpression in squamous cell carcinoma of the esophagus has been found to range from 5% to almost 40% (9,10).

Once HER2 was found to be overexpressed in subgroups of esophageal, esophagogastric, and gastric cancer patients, the next question was whether this oncogene was associated with poorer survival rates as seen in breast cancer. Early institutional studies evaluating HER2 overexpression and long-term overall survival were known for conflicting findings (11,12). In a meta-analysis of operable esophageal cancer patients, it was found that among high-quality analyses, esophageal adenocarcinoma patients with overexpression of HER2 [most commonly defined in early reports as immunohistochemistry (IHC), ≥ 2] had poorer

5-year all-cause mortality (OR 1.9; 95% CI, 1.2–3.2; $P=0.001$) (13). This increased rate of 5-year mortality was also detected for squamous cell esophageal carcinoma (OR 2.9; 95% CI, 1.3–6.2; $P=0.006$) (13). For gastric cancers, previous work has demonstrated that HER2 overexpression ranges from 8–20% (with slightly higher rates for HER3 and HER4), although correlation between expression of the HER2 subtypes has been demonstrated (14,15). Amplification in gastric cancer has been found to be strongly associated with intestinal type adenocarcinoma and significantly reduced overall survival (14,15). Current NCCN guidelines recommend that patients with inoperable locally advanced, recurrent, or metastatic adenocarcinomas of the esophagus, esophagogastric junction, or stomach be considered for tailored therapy in cases of 3+ overexpression by IHC or fluorescence in situ hybridization (FISH) positive (HER2:CEP17 ratio ≥ 2), and patients that are 2+ be additionally examined by FISH (16).

Trastuzumab

After the emergence of trastuzumab as a standard of care for breast cancer patients with HER2 overexpression due to successes in improving overall survival among those with metastatic disease, there was great interest to evaluate its use among other tumor sites (17). Trastuzumab is a monoclonal antibody specific for HER2 that prevents activation of the intracellular kinase activity, with described mechanisms including prevention of HER2 receptor dimerization, endocytic destruction of the receptor, decreased shedding of the extracellular domain, and increased cell-mediated

cytotoxicity (18).

From 2005 to 2009, the Trastuzumab for Gastric Cancer (ToGA) randomized controlled trial evaluated the safety and clinical efficacy of this agent for locally advanced, recurrent or metastatic adenocarcinoma of the gastroesophageal junction or stomach (19). For study entry, patients' tumors were considered to overexpress HER2 if they were scored as 3+ on IHC or were FISH positive (HER2/CEP17 ratio >2). All patients received chemotherapy consisting of either capecitabine plus cisplatin or fluorouracil plus cisplatin every 3 weeks for six cycles, with those being randomized to the study treatment also receiving concurrent trastuzumab. Patients receiving trastuzumab with chemotherapy did have a significant improvement in median overall survival compared to the chemotherapy only arm (13.8 *vs.* 11.1 months), with no difference in grade 3 or 4 adverse events. On exploratory analyses, this improvement in overall survival was even more pronounced among patients with IHC 3+ or IHC 2+ with positive FISH (16.0 *vs.* 11.8 months). Additionally, patients in the trastuzumab and chemotherapy arm experienced longer progression-free survival (6.7 *vs.* 5.5 months) and higher rates of overall tumor response (47% *vs.* 35%). This trial established trastuzumab as a standard of care agent for patients with esophagogastric/gastric adenocarcinoma with HER2 overexpression.

A modification to enhance the effect of HER2 targeted therapy included the development of trastuzumab emtansine, an antibody-drug conjugate. Trastuzumab binds the HER2 receptor as previously described and emtansine (also called DM1) is internalized and inhibits cell division by binding to tubulin, thereby inhibiting microtubule polymerization. This agent was evaluated in the GATSBY randomized controlled trial comparing trastuzumab emtansine with either paclitaxel or docetaxel versus a taxane only in patients with locally advanced/metastatic HER2 positive gastric or gastroesophageal cancer that had shown progression on first line fluoropyrimidine and platinum therapy (20). Of note, the majority of the approximately 400 patients randomized in this trial had received prior HER2 targeted therapy (77%). Ultimately, the novel combination of trastuzumab with emtansine did not result in improvements in overall survival compared to taxane therapy (7.9 *vs.* 8.6 months, $P=0.86$) or median progression-free survival (2.7 *vs.* 2.9 months, $P=0.31$).

As a substantial proportion of patients receive neoadjuvant chemoradiation therapy prior to esophagectomy for locally advanced disease, a logical extension of this neoadjuvant

approach was to add concurrent trastuzumab to standard chemoradiation to the neoadjuvant therapy of patients with HER2 overexpressing tumors. RTOG 1010 is a phase III trial evaluating the addition of trastuzumab to neoadjuvant chemoradiation (paclitaxel and carboplatin with 50.4 Gy at 1.8 Gy/fraction) followed by surgery for esophageal or esophagogastric adenocarcinoma (21). Following recovery from esophagectomy, patients will continue to receive trastuzumab every 3 weeks, for 13 additional doses as maintenance therapy. Currently this multicenter trial has met accrual targets and results are pending.

Lapatinib

While patients with HER2 overexpression experienced a significant survival benefit with trastuzumab, the search for additional HER2 targets with more durable effects continued. One such endeavor was the Lapatinib Optimization Study in HER2-Positive Gastric Cancer (LOGiC) trial, a phase III randomized controlled study to evaluate clinical response of the first oral tyrosine kinase inhibitor of both HER2 and epidermal growth factor receptor (EGFR) in addition to capecitabine and oxaliplatin in patients with unresectable esophageal, gastroesophageal, or gastric adenocarcinoma (22). While there was an improvement in the response rate, no significant difference was detected in median overall survival. On subgroup analysis, while there was no difference in the mortality hazard for the lapatinib arm based on HER2 IHC status, significant improvements were seen in survival for patients under 60 years of age and in Asia. Lapatinib was also evaluated as a second line therapy in addition to weekly paclitaxel (TyTAN trial) in Asian patients with disease progression following gastric cancer therapy with HER2 overexpression (23). Again, while response rates were improved, there was no significant difference found in progression-free survival or overall survival. These negative studies have distinguished gastroesophageal cancers from breast cancers where these approaches yielded improved outcomes for patients. Additionally, in breast cancer, HER2 treatment is continued beyond tumor progression with first-line therapy; this strategy has not been proven successful in treating gastroesophageal cancers.

Pertuzumab

Recently, pertuzumab has evolved as another possible adjunct therapy for HER2 overexpressing malignancies.

Pertuzumab binds to a different epitope of the HER2 extracellular domain, ultimately preventing dimerization with other receptors in the HER family, in addition to the stimulation of cell-mediated cytotoxicity that trastuzumab was known to cause (24). A randomized controlled trial in patients with HER2 positive metastatic breast cancer which compared pertuzumab with trastuzumab to trastuzumab alone (with both arms receiving docetaxel) found that patients in the pertuzumab and trastuzumab arm had significantly longer median progression-free survival with similar safety profiles (25). Work evaluating pertuzumab for esophageal and gastric cancer patients is also underway. A phase IIA trial examining administration of pertuzumab in addition to trastuzumab, capecitabine, and cisplatin in patients with locally advanced, inoperable, or metastatic HER2 positive adenocarcinoma of the gastroesophageal junction or stomach (JOSHUA) established dosing parameters and established the safety profile for a phase III evaluation (JACOB), which is currently ongoing at over 190 study centers (26,27). This agent is additionally being evaluated in a novel neoadjuvant regimen: the TRAP trial (Study of Chemoradiation, Trastuzumab, and Pertuzumab in Resectable HER2+ Esophageal Carcinoma) which is seeking to establish the feasibility of this multimodality neoadjuvant regimen and its impact on pathologic response, surgical margins, and postoperative complications (28).

HER1/EGFR targeted therapies

Gene amplification and overexpression of EGFR (or HER1) has also been documented in several malignancies including esophageal, esophagogastric, and gastric tumors. EGFR is a transmembrane protein that also has tyrosine kinase activity in the presence of ligands such as epidermal growth factor and transforming growth factor- α (29). Previous work has demonstrated that increased EGFR expression (2+ or 3+) is present in over 30% of esophageal and esophagogastric adenocarcinomas, and was associated with higher pathologic T, N, and M stage (30). In esophageal squamous cell cancer, even higher rates of EGFR overexpression have been documented, with some studies exceeding 70%, and have also been correlated with more advanced pathologic stages and poorer overall survival (31,32).

Cetuximab

Cetuximab, a chimeric monoclonal antibody targeted against EGFR, had shown efficacy in certain groups of metastatic

head and neck, colon, and lung cancers and was eventually tested in patients with esophageal and gastric malignancies (33-35). The EXPAND trial evaluated cetuximab in the setting of capecitabine and cisplatin for patients with locally advanced or metastatic adenocarcinoma of the gastroesophageal junction or stomach, at over 100 sites in 25 countries (36). Unfortunately, there was no significant improvement in progression-free survival, and a higher rate of grade 3-4 adverse events in patients receiving cetuximab compared to those receiving capecitabine and cisplatin alone.

Panitumumab

The REAL3 phase III trial (epirubicin, oxaliplatin, and capecitabine with or without panitumumab) which evaluated an alternate EGFR inhibitor in patients with locally advanced inoperable or metastatic esophageal cancer (without molecular testing) actually found an increased mortality hazard among patients in the panitumumab arm (n=254) (37).

However, questions remained if there may be a benefit of EGFR inhibitors to select patient populations. For example, it is known that radiation therapy can increase EGFR expression in tumors, as well as increase the TGF α activation of the receptor, so recent phase II and phase III trials have sought to evaluate the effect of EGFR inhibitors during concurrent radiation therapy, as a means to improve local control and response rates (38). However, a phase II trial of preoperative chemoradiation with concurrent panitumumab in patients with resectable esophageal cancer (the PACT study) did not improve the pathologic complete response (pCR) rate past the pre-defined goal of 40% (39). Similarly, ACOSOG Z4051, which was a phase II trial evaluating a neoadjuvant regimen of docetaxel, cisplatin, panitumumab, and 50.4 Gy in 1.8 Gy/fraction, followed by esophagectomy, achieved a pCR rate of 33.3%, but did not reach the primary objective of a pCR rate of $\geq 35\%$ (40). Additionally, almost half of patients experienced a toxicity of ≥ 4 . Given EGFR inhibitors' lack of efficacy, and evidence of possible harm in some patient groups, this family of agents has largely been abandoned for esophageal and gastric malignancies until improved techniques to select appropriate patients that may benefit from these agents can be identified and validated.

Vascular endothelial growth factor (VEGF) targeted therapies

Similar to other tumor types, the pathways of neoangiogenesis

have been considered as potential targets in esophageal and gastric cancer. The VEGF family has long been documented to regulate tumor angiogenesis and lymphangiogenesis. However, it has been challenging to determine which specific tumor profiles may benefit the most from VEGF inhibitors. While not routinely used in most clinical practices, possible surrogates of VEGF activity (and potential markers of response to VEGF inhibitors) have included high tumor microvessel count (MVC), high proliferating cell nuclear antigen (PCNA), VEGF:basic fibroblastic growth factor (bFGF) ratio, as well as VEGF polymorphism subtyping (41). However, given the fact that activity of the VEGF family nearly ubiquitously stimulates angiogenesis to promote tumor growth, survival, and eventually migration, VEGF inhibitors have been assessed in many tumor types in the absence of specific tumor marker categorization.

Bevacizumab

One of the agents investigated in this family was bevacizumab, a VEGF-A inhibitor. The AVAGAST phase III trial evaluated bevacizumab in combination with cisplatin and capecitabine (or fluorouracil) for patients with previously untreated locally advanced or metastatic adenocarcinoma of the gastroesophageal junction or stomach (42). While the addition of bevacizumab to first-line chemotherapy did not result in improvements in overall survival, a significant improvement in progression-free survival (6.7 *vs.* 5.3 months) and overall response rate (46% *vs.* 37.4%) was detected. On subgroup analysis, significant decreases in overall mortality hazard was detected for patients from North or South America (but not for European or Asian patients) and for those patients with locally advanced disease (but not with metastatic disease). A latter study of blood and tissue markers from patients in the AVAGAST trial demonstrated that patients with higher baseline levels of VEGF-A and lower levels of neuropilin-1 (a transmembrane glycoprotein) were more sensitive to bevacizumab treatment with significant improvements in overall survival (43). Of note, this finding still showed geographic variation, with Asian patients not demonstrating the same benefit with bevacizumab, despite high VEGF-A levels.

Ramucirumab

Ramucirumab, a VEGFR-2 inhibitor that prevents VEGF binding in endothelial cells, was assessed as a second line therapy after platinum or fluoropyrimidine therapy

for recurrent or metastatic gastroesophageal junction or gastric cancer (REGARD) (44). In this multicenter trial, improvements in median overall survival did reach significance (5.2 months for the ramucirumab arm *vs.* 3.8 months in the placebo arm), as did the improvement in median progression free survival (2.1 *vs.* 1.3 months, respectively). Ramucirumab was further evaluated with concurrent paclitaxel in locally advanced or metastatic esophagogastric or gastric adenocarcinoma with evidence of disease progression after first line chemotherapy (platinum and fluoropyrimidine doublet, with or without anthracycline), in the phase III RAINBOW trial (45). Compared to the paclitaxel only arm, patients that also received ramucirumab experienced longer median overall survival (9.6 *vs.* 7.4 months). Of note, patients in the combined ramucirumab and paclitaxel arm did experience higher rates of selected Grade 3 or higher adverse events including neutropenia, leucopenia, and hypertension. However, based on these findings, ramucirumab is now a preferred second-line therapy for metastatic or locally advanced esophagogastric or gastric adenocarcinoma (category 1 recommendation from the NCCN) and esophageal adenocarcinoma (category 2A) (16). Evaluation of ramucirumab as a first-line agent to date has not been endorsed. A multicenter phase II trial evaluating ramucirumab with leucovorin, fluorouracil, oxaliplatin (FOLFOX) in patients with previously untreated locally advanced or metastatic unresectable gastroesophageal or gastric adenocarcinoma found no difference compared to FOLFOX with placebo for median progression free survival (6.4 *vs.* 6.7 months) or overall survival 11.7 *vs.* 11.5 months (46). Of note, this trial had a relatively high proportion of esophageal adenocarcinomas in each arm (46% in the ramucirumab and FOLFOX group and 49% in the FOLFOX/placebo group), and was conducted at centers in the United States only. While the progression free survival rate was significantly higher at 3 months for the ramucirumab and FOLFOX patients (89% *vs.* 75%, $P=0.02$), this did not persist at 6, 9, or 12 months. A phase III randomized trial (RAINFALL) is currently in progress to assess ramucirumab as a first-line agent with cisplatin and capecitabine or 5-FU in HER2 negative metastatic gastroesophageal or gastric adenocarcinoma patients at over 130 centers globally (47).

Apatinib

The most recently assessed VEGF inhibitor for gastric

malignancy is apatinib, a tyrosine kinase inhibitor that demonstrates strong affinity and selectivity for VEGFR-2. A phase II trial of apatinib for advanced or metastatic esophagogastric or gastric adenocarcinoma refractory to at least two chemotherapeutic agents (including platinum and fluoropyrimidine agents) demonstrated improvements in both median overall survival (4.8 *vs.* 2.5 months in the placebo arm) and progression free survival (3.7 *vs.* 1.4 months respectively) (48). Based on these promising results from the phase II study, once daily oral dosing of apatinib (with a treatment cycle of 28 days) was selected for comparison to placebo in a multicenter randomized controlled trial at over 30 centers in China (49). Again, advanced or metastatic gastric adenocarcinoma patients in the apatinib arm experienced improved median overall survival compared to placebo (6.5 *vs.* 4.7 months) and longer progression free survival (2.6 *vs.* 1.8 months, respectively). Apatinib was generally well tolerated in this trial, with 8.5% experiencing grade 3 or 4 hand-foot skin reaction, 4.5% grade 3 or 4 hypertension, and 2.3% grade 3 or 4 proteinuria. At this time, apatinib is not approved for use in the U.S.

c-Met Targeted Therapy

c-Met (mesenchymal-epithelial transition factor) is a transmembrane tyrosine kinase receptor that is activated upon binding the hepatocyte growth factor (HGF) with overexpression being associated with poorer survival in gastric cancer as well as other malignancies (50). While c-Met overexpression has been documented with relatively low rates among gastric malignancies (approximately 10%), this value is remarkably high among esophageal squamous cell cancers at almost 70% (51). Previous work has shown that esophageal squamous cell tumors with c-Met overexpression demonstrate a correlation with increasing tumor depth and pathologic stage, and is independently associated with poorer 5-year overall survival (51).

Foretinib

Additionally, relevant to esophageal and gastric malignancies is the finding that activation of c-Met pathways may occur in the setting of HER2 targeted therapy. Specifically, description of c-Met/HGF activation causing escape of tumor cells from lapatinib-induced growth inhibition in HER2 amplified gastric cancer cells has been reported (52). Similarly, c-Met amplification has been associated with resistance to EGFR therapy (erlotinib, gefitinib) in lung

cancer patients (53). As such, potential c-Met inhibitors have been a focus of active research. One such development has been foretinib, an oral multikinase inhibitor (with targets including c-Met, VEGFR, RON, and AXL), that has had promising results in reversing the HGF induced escape mechanisms from lapatinib and erlotinib therapy (54). Recently, a phase II trial did not show any efficacy in overall response rate, progression free survival, or overall survival for foretinib alone among poorly differentiated locally advanced or metastatic gastric adenocarcinoma patients, but has not yet been evaluated in conjunction with HER2 targeted therapy, or among esophageal squamous cell patients, where the prevalence of c-Met overexpression is higher (55).

Onartuzumab

Results of a phase II trial of onartuzumab, a monoclonal antibody with activity against c-Met in conjunction with FOLFOX6 for advanced gastroesophageal cancer demonstrated no difference in the primary end-point (progression-free survival) (56). Of note, approximately 30% of patients in each arm were c-Met positive patients ($\geq 50\%$ of tumor with moderate to strong intensity staining on IHC), and even among this enriched subgroup, no benefit was detected. In a phase III trial with metastatic HER2 negative, c-Met positive gastroesophageal cancer patients again comparing first line FOLFOX6 to FOLFOX6 with onartuzumab (METGastric), no difference in overall survival was detected for the enrolled group or among strongly (2+, 3+) c-MET positive patients (57). Exploratory subgroup analyses did show improved overall survival among non-Asian patients and in patients without gastrectomy, with any c-MET status.

Rilotumumab

In an alternative effort to interfere with the c-MET HGF pathway, rilotumumab was developed as a human monoclonal antibody with high affinity for HGF, thereby preventing it from binding to the c-MET receptor. A phase II trial examining the use of rilotumumab with epirubicin, cisplatin, and capecitabine for first-line treatment of locally advanced or metastatic gastroesophageal or gastric adenocarcinoma, suggested an improvement in progression free survival events for patients receiving rilotumumab versus placebo (58). Based on these findings, a phase III trial was developed (RILOMET-1), but was stopped early secondary to increased mortality in the rilotumumab arm (59). Patients in the rilotumumab arm had poorer

overall survival (9.6 *vs.* 11.5 months, $P=0.016$) and objective response rate (30% *vs.* 39.2%, $P=0.03$). On subgroup analysis, rilotumumab was still not associated with any improvement in survival, even for patients with $\geq 1+$ c-MET expression. With these findings, the use of rilotumumab in other clinical trials was halted as well.

Mechanistic target of rapamycin (mTOR) targeted therapy

mTOR is a protein kinase with an impressive array of cellular functions when activated, including cell proliferation, growth, transcription, and protein synthesis. Pathologic comparisons of gastric adenocarcinoma to normal gastric mucosa have demonstrated increased expression of mTOR in tumor samples, as well as upstream proteins known to activate mTOR, such as PI3K and AKT (60). PTEN, a known regulator of mTOR activation (by inhibiting the PI3K/AKT/mTOR pathway) has been found to be significantly lower in gastric tumor samples. Further work established the correlation between increased cytoplasmic mTOR expression and depth of gastric adenocarcinoma invasion, lymph node involvement, more advanced tumor stage, poorer relapse-free survival and overall survival (61). Alternatively, nuclear mTOR expression was negatively correlated with tumor invasiveness and poorer survival outcomes.

Everolimus

Everolimus has long been used as an oral mTOR inhibitor in solid organ transplant patients as an immunosuppressive agent, but began to gather attention as a novel agent for renal cell carcinoma, pancreatic neuroendocrine tumors, and select breast cancer patients (ER/PR positive, HER2 negative). A phase II study of everolimus (with standard dosing of 10 mg daily) as a second-line agent for patients with advanced gastric adenocarcinoma who had demonstrated progression on prior chemotherapy showed a promising disease control rate of 56% and median progression-free survival of 2.7 months (62). However, a phase III trial of everolimus in the same patient population (GRANITE-1) approached, but did not reach significance in median overall survival between the everolimus arm and the placebo group (5.4 *vs.* 4.3 months, $P=0.12$) (63).

Immunotherapy targets

With breakthrough agents in the realm of immunomodulation

therapy for melanoma, lymphoma and other malignancies, attention has begun to shift to the possible role and efficacy of immune checkpoint inhibitors for gastrointestinal cancers. One approach that is currently at the forefront of such research is blocking the interaction between T-cells and tumor cells through programmed death-1 receptor-ligand binding. While this interaction inhibits T-cell costimulation and facilitates evasion of the tumor cell from the immune system, targeted inhibitors can block the binding of the cytotoxic T-cell receptor to the tumor cell programmed death-1 ligand (PDL1) (64). Anti-PD1 therapy has already demonstrated impressive and durable improvements in clinical responses in patients with melanoma, non-small cell lung cancer, and renal cell carcinoma (65-67). Features that make gastroesophageal cancers attractive for this type of checkpoint therapy include high rates of somatic mutations as well as the identification of gastric cancer subtypes with high PD-L1 expression (68,69).

Pembrolizumab

Previous analysis of tumor samples from stage II and III gastric cancer patients has demonstrated that PDL1 overexpression was observed in approximately 30% of patients, and was independently associated with poorer overall survival, suggesting that this may be an actionable target for subgroups of patients with these tumors (70). The KEYNOTE-012 phase Ib trial was a multicenter study that evaluated pembrolizumab, a humanized antibody against PD-1, in patients with a variety of malignancies including advanced gastric, urothelial, head and neck, and triple negative breast cancer (71). Patients were eligible for entry into the gastric cancer cohort if they were determined to have PD-L1 positive recurrent or metastatic adenocarcinoma of the gastroesophageal junction or stomach (after any therapy type, but excluding previous treatment with other immune checkpoint inhibitors), and were given pembrolizumab every 2 weeks for 24 months or until disease progression, death, toxicity, or study withdrawal. PDL1 positivity was initially assessed by membrane staining in at least 1% of cells in a section of archived tumor cells and then re-evaluated with a prototype immunohistochemistry assay that assigned PDL1 density scores to both the tumor cells as well as mononuclear inflammatory cells. Of the 162 patients screened, 40% demonstrated PD-L1 positivity (72).

Of the 36 patients in the gastric malignancy cohort of the KEYNOTE-012 trial that were able to be evaluated, 22% (95% CI, 10–39%) demonstrated partial response

to pembrolizumab with a median duration of response of 40 weeks, with 4 patients continuing to have no evidence of disease progression. No patients in the study achieved a complete response rate. This response rate was similar between Asian institutions and other geographic centers. Of note, patients with a higher mononuclear inflammatory PDL1 cell density score experienced a higher partial response rate (score 3: 44%) than patients with a high tumor PDL1 proportion (50–100%: 33%). No treatment-related treatment discontinuation or deaths occurred, and only 13% of patients experienced grade 3 (fatigue, pemphigoid, hypothyroidism, peripheral neuropathy) or 4 (pneumonitis) complications. Median overall survival was 11.4 months (95% CI, 5.7–not reached). Interestingly, 8 patient biopsies assessed at the time of data completion had essentially negative PDL1 status (mononuclear inflammatory PDL1 cell density score of 1 or less and tumor PDL1 proportion of 0), possibly suggesting changes in PDL1 expression following treatment with pembrolizumab or heterogeneity of the gastric tumors (73).

Recently, pembrolizumab was also evaluated in esophageal cancer (squamous cell or adenocarcinoma histology) as a phase Ib trial in patients with a similar PD-L1 positivity and treatment regimen as described in KEYNOTE-012 (74). In this trial, 41% of enrolled esophageal cancer patients demonstrated PD-L1 positivity, with a patient population that skewed to squamous cell (77%). Of note, the majority (87%) of patients had received two or more previous types of systemic therapy prior to participation in the study. Objective response rate in this trial was 23%, with no drug related adverse events greater than grade 3. Currently, the phase II KEYNOTE-180 study is also evaluating pembrolizumab in advanced or metastatic esophageal adenocarcinoma or squamous cell cancer that has progressed on two prior agents (including trastuzumab if HER2 positive) (75).

Nivolumab

Nivolumab, another human monoclonal antibody targeted against PD-1 with efficacy demonstrated in various malignancies including melanoma and non-small cell lung cancer has also been considered for upper gastrointestinal tumors. Reports from a phase I/II trial (part of the CheckMate-032 study) with 59 advanced or metastatic gastroesophageal or gastric cancer patients treated with single agent nivolumab demonstrated an objective response rate of 12%, with one complete response and

6 partial responses (76). Of note, 39% of tumor samples were classified as PD-L1 positive, with a higher objective response rate (18%). About 21% of patients were noted to have stable disease. Given these findings, it is feasible that nivolumab may be considered for further evaluation in a randomized controlled trial.

Conclusions and future directions

While advanced esophageal, esophagogastric, and gastric malignancies continue to have a prominent global presence with poor 5-year survival outcomes, significant gains are starting to be made with the use of targeted biologic therapies. In the near future, the evaluation and clinical use of these agents will be greatly assisted by comprehensive characterizations and subclassifications of gastric and related GI malignancies. This massive effort is already underway in projects such as The Cancer Genome Atlas Research Network (TCGA) which is working to organize gastric malignancies into four subtypes each with a distinct and relatively predictable mutation profiles: Ebstain-Barr positive tumors, genomically stable tumors, tumors with microsatellite instability, and tumors with chromosomal instability (77).

While not all agents (EGFR inhibitors) have demonstrated the same efficacy in esophageal and gastric malignancies that they have accomplished for other tumor types, others are now employed as recommended agents in progressive or refractory disease (trastuzumab and ramucirumab). Others, such as lapatinib, onartuzumab, and bevacizumab, may demonstrate improved efficacy among specific geographic populations and warrant further tailored investigation. Furthermore, the potential agents for immunomodulation therapy continue to expand and pose exciting developments for esophageal and gastric malignancies. While the pace of biologic therapies, including immunotherapy agents, in phase I, II, and III trials continue at a fervent pace, important components to contextualize these studies will include the role of potential biomarkers to guide tailored therapy, as well as decision and cost-effectiveness analyses to assist in determining which agents will impart the most substantial and meaningful benefits.

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Footnote

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