Genomic Alterations in Advanced Esophageal Cancer May Lead to Subtype-Specific Therapies

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Esophageal cancer • Genomic • Mutation • HER2 • Novel • Targeted • Therapy

Learning Objectives

Describe the current status of targeted therapy for esophageal cancer.

Describe the molecular aberrations which are thought to drive the development and spread of esophageal cancer in order to identify promising targets for specific inhibition.

ABSTRACT

The development of targeted agents for metastatic esophageal or gastroesophageal junction (GEJ) tumors has been limited when compared with that for other common tumors. To date, the anti-human epidermal growth factor receptor-2 (HER-2) antibody, trastuzumab, in combination with chemotherapy, is the only approved novel agent for these cancers, and its use is limited to the small population of patients whose tumors overexpress HER-2. Despite recent progress in the field, median overall survival remains only 8–12 months for patients with stage IV esophageal or GEJ cancer. In this article, we examine the molecular aberrations thought to drive the development and spread of esophageal cancer and identify

promising targets for specific tumor inhibition. Data from clinical studies of targeted agents are reviewed, including epidermal growth factor receptor antibodies, tyrosine kinase inhibitors, HER-2, and vascular endothelial growth factor-directed therapy. Current and future targets include MET, fibroblast growth factor receptor, and immune-based therapies. Evidence from trials to date suggests that molecularly unselected patient cohorts derive minimal benefit from most target-specific agents, suggesting that future collaborative investigation should focus on preselected molecular subgroups of patients with this challenging heterogeneous disease. *The Oncologist* 2013;18:823–832

Implications for Practice: The disease burden of esophageal cancer is increasing in the United States and worldwide, primarily driven by higher rates of adenocarcinoma risk factors, including obesity and Barrett's esophagus. Chemotherapy has moderate efficacy for locally advanced and metastatic esophageal cancer, but new approaches to treatment are urgently needed. This article focuses on potential oncogenic targets in esophageal cancer and comprehensively reviews the current state of the art in targeted therapy for esophageal and gastroesophageal junction tumors. Anti-human epidermal growth factor receptor-2 therapy has provided benefit for a small proportion of patients; however, despite signs of efficacy in early phase clinical trials, results with anti-epidermal growth factor receptor and anti-vascular endothelial growth factor therapy have been generally disappointing. Experience to date with targeted agents suggests that collaborative trials of target-specific agents in those subgroups of patients who have potential oncogenic drivers represent the best opportunity for bringing novel agents to the clinic.

INTRODUCTION

The incidence of esophageal cancer is increasing rapidly. In the United States and worldwide, there are more than 400,000 deaths from esophageal cancer annually [1, 2]. Although progress has been made in refining trimodality therapy for localized and locally advanced esophageal cancer, most notably with the recent CROSS study, development of targeted agents for esophageal cancer has lagged behind that of many other solid tumor types. With currently available therapies, the prognosis for those with advanced esophageal or gastroesophageal junction (GEJ) tumors remains extremely poor [1, 3]. Recent genomic sequenc-

ing of esophageal cancer suggests that although potential driver mutations occur infrequently, copy number alterations are more common and, for selected patients, may represent potential targets using currently available investigational agents [4, 5]. In this article, we review previous attempts to develop target-specific agents for esophageal and GEJ tumors, many of which have unfortunately been unsuccessful. Lessons from these experiences are explored and results of the recent phase III REGARD clinical trial, which demonstrated the efficacy of a novel vascular endothelial growth factor 2 (VEGFR2) monoclonal antibody, ramuci-

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rumab, in the second-line gastroesophageal setting, are discussed. Finally, we identify some novel agents that have recently entered into clinical investigation and may hold some promise.

MATERIALS AND METHODS

Data from PubMed and Medline databases were obtained using the search terms “molecular esophageal,” “targeted therapy esophageal and gastroesophageal,” and several other target-specific search terms (e.g., “HER-2 [human epidermal growth factor receptor-2] esophageal”). Relevant clinical trials of targeted therapy for esophageal or GEJ cancer were found by searching the PubMed and Medline databases and the abstracts of the American Society of Clinical Oncology Annual Meetings and Gastrointestinal Symposia and abstracts presented at the European Society of Medical Oncology Annual Meeting. The time period searched was from 2000 to 2013.

Molecular Biology of Esophageal Cancer

The increasing incidence of distal esophageal and junctional adenocarcinoma is thought to be secondary to escalating rates of gastroesophageal reflux disease and Barrett's esophagus. Although there is a paucity of data, the existence of familial cancer syndromes such as tylosis and hereditary diffuse gastric cancer suggest that inherited factors may play a role in disease development. Multiple low-penetrance susceptibility genes have been suggested to be involved in the development of both esophageal squamous cell cancers and adenocarcinomas, although our current understanding of the impact of these genes remains limited. Most of the candidate gene studies of squamous cell carcinomas involve genes responsible for alcohol metabolism, detoxification of xenobiotics, and folate metabolism. Alcohol dehydrogenase 1B (*ADH1B*) and acetaldehyde dehydrogenase 2 (*ALDH2*) polymorphisms have been associated with increased risk for these cancers [6]. A number of studies have investigated whether polymorphisms in phase 1 and 2 enzymes can alter the metabolic activation and detoxification of xenobiotics. To date, only cytochrome p450 1A1 (*CYP1A1*)-linked polymorphisms are consistently associated with an increased risk for squamous cell esophageal carcinoma [7, 8]. Significant numbers of gene-association studies in esophageal adenocarcinoma are lacking, but a number of small observational studies in families affected by Barrett's esophagus and esophageal adenocarcinoma suggest there may be an underlying genetic susceptibility [9–12]. There are few data identifying culprit genes, but it has been suggested that, as occurs with squamous cell cancers, polymorphisms in enzymes responsible for detoxification of luminal toxic agents and xenobiotics might lead to an increased risk. Glutathione S-transferase (GST) enzymes play an important role in cellular protection against oxidative stress and toxic foreign chemicals. It has been suggested that the allelic variants of GST (*GSTP1*, *GSTM1*, and *GSTT1*) might influence susceptibility to Barrett's esophagus; however, to date the data are inconclusive [13–15]. Furthermore, there are contradictory reports regarding the importance of cyclin D1 polymorphisms in the development of Barrett's esophagus [16, 17].

Chromosomal aberrations leading to gene dysregulation have been reported in esophageal cancer. Amplifications on 8q and 17q map to the *C-MYC* and *ERBB2* (*HER-2*) oncogenes

The knowledge that EGFR is overexpressed and correlated with a poor prognosis has spurred numerous clinical studies of agents, including tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs) targeting EGFR in esophageal or GEJ cancer. Given the low incidence of activating mutations of EGFR in esophageal cancer, it is not surprising that studies of EGFR TKIs to date have been disappointing, with relatively high toxicity rates and few clear signals of activity.

[18, 19]. Targeting *HER-2* is now the standard of care in treating patients with stage IV gastroesophageal cancer when amplification is confirmed [20]. The role of *MYC* in the pathogenesis of esophageal cancer is not as well-defined, and additional research is required. Loss of heterozygosity of TP53 occurs in greater than 50% of cases and is considered a strong predictor of disease progression [21–23]. In addition, two genes reported to have homozygous deletions in esophageal cancer are *p16/CDKN2A* and *FHIT* [24]. Inactivation of the tumor suppressor gene *p16INK4A/CDKN2A* occurs by three different mechanisms: hypermethylation of the gene promoter, intragenic mutation coupled with loss of the second allele, and homozygous deletion [24]. DNA copy number gains/amplifications on chromosomes 1q, 3q, 7p, 7q, 8q, 17q, and 20q have been identified in recent years. Copy number losses on 3p, 4q, 5q, 9p, 14q, 16q, 17p, and 18q have been also been reported in esophageal cancer [25]. Goh et al. performed an integrative analysis of array-comparative genomic hybridization and matched gene expression profiling to reveal novel genes with prognostic significance in esophageal adenocarcinomas [25]. Using long-term clinical follow-up data, the authors identified 17 common regions (>5%) of gain and 11 common regions of losses in 56 resected specimens. Novel regions identified included loci 11p13 and 21q21.2. Genes with high copy number and expression correlations included two deletions (*p16/CDKN2*, *MBNL1*) and four gains (*EGFR*, *WT1*, *NEIL2*, *MTMR9*). These genes individually ($p < .060$) and collectively ($p = .008$) had prognostic significance.

A host of additional genes have been studied for the presence of mutations in esophageal cancer, but very few mutations have been identified in most of these studies of single genes. In an effort to perform a comprehensive evaluation of all coding regions for mutations, Agrawal et al. performed a comprehensive study of esophageal cancer exomes, including both adenocarcinomas and squamous cell carcinomas [26]. Inactivating mutations of *NOTCH1* were identified in 21% of esophageal squamous cell carcinomas but not in adenocarcinomas. Dulak et al. conducted an analysis of somatic copy-number alterations using high-density genomic profiling arrays in 296 esophageal and gastric cancers [27]. Amplified genes were noted in 37% of gastric/esophageal tumors, including *ERBB2*, *FGFR1*, *FGFR2*, *EGFR*, and *MET*, suggesting that some of these may be viable targets in esophageal cancer, although amplification of some may be more prevalent in gastric tumors.

Table 1. Selected studies of EGFR-directed therapy in localized or locally advanced esophageal cancer

Phase	NCT identifier	Patient population	Regimen(s)	Outcome or status
Cetuximab				
IB/II	NCT00445861	Stage IIB-IIIC resectable esophageal/GEJ tumors	Preoperative cisplatin/docetaxel/cetuximab	Completed; pCR and near pCR 68% [36]
II	NCT00551759 (E2205)	Stage IA-IIIC resectable esophageal/GEJ adenocarcinoma	Preoperative cetuximab/5-FU/oxaliplatin/radiation Postoperative cetuximab/docetaxel	Closed because of excess pulmonary toxicity
II	NCT00544362	Stage II-III esophageal/GEJ tumors	Cisplatin/5-FU/cetuximab	Completed; pCR not increased [37]
II	NCT00578201	Stage III esophageal squamous tumors	Preoperative 5-FU/leucovorin/oxaliplatin/cetuximab for 2 cycles followed by 5-FU/leucovorin/oxaliplatin/cetuximab/radiation plus or minus surgery	ORR 77.2%, median PFS 13.8 mo, OS 21.6 mo [38]
II	NCT00815308	Stage II-III esophageal squamous tumors not candidates for surgery	Cisplatin/paclitaxel/radiation/cetuximab	ORR 97.7%, median PFS 13.9 mo, median OS 16.8 mo [39]
II	NCT00109850 (SWOG 0414)	Stage III esophageal/GEJ tumors not candidates for surgery	Cisplatin/irinotecan/cetuximab/radiation	Closed early because of poor accrual; 2 deaths caused by study treatment in 21 patients [40]
III	NCT01107639	Stage IIB-IIIC resectable esophageal/GEJ tumors	Preoperative cisplatin/docetaxel/cetuximab/radiation followed by postoperative cetuximab versus CRT alone	Currently accruing
III	NCT00655876	Stage IIA-IV (M1a) esophageal/GEJ tumors	Preoperative paclitaxel/cisplatin/radiation plus or minus cetuximab	Adeno arm closed for futility; squamous arm recruiting
II/III	NCT00509561	Stage IA-IIIC esophageal/GEJ (type 1) tumors not candidates for surgery	Cisplatin/capecitabine/radiation plus or minus cetuximab	Completed; increased toxicity and poorer survival in cetuximab arm (22 mo versus 25 mo, $P = .04$) [41]
Panitumumab				
II	NCT01077999	Stage IA-IIIB resectable esophageal/GEJ tumors	Preoperative carboplatin/paclitaxel/radiation/panitumumab	Completed; pCR not increased [42]
II	NCT00757172 (ACOSOG Z4051)	Stage IIB-IV (M1a) esophageal/GEJ adenocarcinoma	Preoperative cisplatin/docetaxel/radiation/panitumumab	Completed; pCR and near pCR 55.2% [43]
EGFR TKIs				
II	NCT00258323	Stage IIIA-IV (M1a) resectable esophageal/GEJ tumors	Preoperative cisplatin/fluorouracil/radiation/gefitinib followed by postoperative gefitinib	3-yr OS 42% versus 18% in historical control, $P = .0635$
I/II	NCT00393068	Stage I-III resectable esophageal/GEJ tumors	Preoperative carboplatin/paclitaxel/bevacizumab/erlotinib followed by planned postoperative erlotinib/bevacizumab	Median OS 18.4 mo, 29% grade 3–4 esophagitis Postoperative erlotinib/bevacizumab not feasible [44]
Trastuzumab				
II	NCT01748773	Stage IB-IIIB HER-2-positive esophageal/GEJ adenocarcinoma	Postoperative capecitabine/oxaliplatin/radiation/trastuzumab	Currently accruing
III	NCT01196390	Stage IB-IIIB HER-2-positive esophageal/GEJ adenocarcinoma	Preoperative carboplatin/paclitaxel/trastuzumab followed by postoperative trastuzumab versus preoperative carboplatin/paclitaxel followed by postoperative trastuzumab	Currently accruing
Lapatinib				
II	NCT01769508	Stage I-III HER-2-positive esophageal/GEJ/gastric adenocarcinoma	5-FU/leucovorin/oxaliplatin/radiation/lapatinib	Pending activation

Abbreviations: 5-FU, 5-fluorouracil; CRT, chemoradiation; EGFR, epidermal growth factor receptor; GEJ, gastro-esophageal junction; HER-2, human epidermal growth factor receptor-2; m, months; NCT, clinicaltrials.gov identifier; ORR, overall response rate; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; SWOG, Southwest Oncology Group; TKI, tyrosine kinase inhibitor.

Targeted Therapies

EGFR

When assessed by immunohistochemistry, epidermal growth factor receptor (EGFR) is overexpressed in 32%–65% of esophageal or GEJ tumors [28–31] and independently predicts poor prognosis [29–32]. Mutations of EGFR are uncommon in esophageal or GEJ tumors, with reported rates ranging from 0% in European studies to 12%–14% in studies from Asia [33, 34]. The knowledge that EGFR is overexpressed and correlated with a poor prognosis has spurred numerous clinical studies of agents, including tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs) targeting EGFR in esophageal or GEJ cancer (Table 1).

Given the low incidence of activating mutations of EGFR in esophageal cancer, it is not surprising that studies of EGFR TKIs to date have been disappointing, with relatively high toxicity rates and few clear signals of activity. In a phase II study of multimodality therapy for locally advanced esophageal cancer that combined gefitinib with preoperative 5-fluorouracil (5-FU)/cisplatin and radiation, a trend toward improved 3-year overall survival (OS) was noted for patients who received gefitinib; however, it did not reach statistical significance (40% vs. 28%, $p = .06$), and postoperative gefitinib was poorly tolerated [35]. In a phase II second-line study of single-agent gefitinib for advanced esophageal

cancer, a single partial response was noted from 36 treated patients (2.8%), and in another single-agent phase II study, three partial responses were seen in 27 patients (11.1%) with advanced unresectable esophageal adenocarcinoma. In both studies, median progression-free survival (PFS) was less than 2 months [45, 46]. Similarly, erlotinib has limited activity. In a phase II Southwest Oncology Group (SWOG) study that included 44 patients with advanced GEJ tumors, an objective response rate (ORR) of 9% was noted, and median PFS was 2 months. No mutations in EGFR were found [47].

Cetuximab, an mAb targeting EGFR, is the most widely studied targeted agent in esophageal cancer. Despite early promise, with pathologic complete response (pCR) and near pCR rates of 68% in a phase IB study [36], phase II and III studies to date have been disappointing (Table 1). The phase II study, SWOG 0414, examined definitive therapy for locally advanced esophageal cancer with cisplatin/irinotecan/cetuximab and radiation [40]. This study closed early because of poor accrual. Significant toxicity was also noted, with two treatment-related deaths in 21 patients enrolled. The adenocarcinoma arm of a phase III RTOG study that randomly assigned patients to preoperative cisplatin/paclitaxel/radiation with or without cetuximab has recently closed because of futility; however, the study continues to accrue patients with squamous histology. The Swiss phase III study, NCT01107639, is adding cetuximab to preoperative chemoradiation (CRT) and is attempting to administer maintenance cetuximab in the postoperative setting. Recently, however, a phase II/III study conducted in the United Kingdom has demonstrated significantly increased toxicity and inferior survival associated with the addition of cetuximab to definitive CRT [41]. The fully human mAb against EGFR, panitumumab, demonstrated promising pCR and near pCR rates in a phase II ACOSOG study; however, the phase III REAL-3 study has recently closed for lack of efficacy, and the future for this agent in esophageal cancer is unclear [43]. Taken as a whole, the results of studies with cetuximab and panitumumab seem ominous for the future role of EGFR mAbs in the treatment of esophageal cancer unless a dependable biomarker for efficacy can be developed, bearing in mind the significant toxicity and limited efficacy reported to date.

HER-2

HER-2, which is overexpressed in only 12%–14% of esophageal adenocarcinomas and rarely in squamous histologies, may be correlated with a poor overall prognosis [48, 49]. The first-line phase III ToGA study compared cisplatin/fluoropyrimidine chemotherapy with or without trastuzumab for metastatic gastric or GEJ tumors overexpressing HER-2. In this study, 18% of patients had GEJ tumors [50]. A total of 594 patients were enrolled in the study, and slightly greater than one in five patients (22.1%) screened had HER-2-positive tumors by immunohistochemistry or fluorescence in situ hybridization. This study demonstrated a 2.7-month OS advantage with the addition of trastuzumab to chemotherapy (13.8 months vs. 11.1 months, $p = .0046$) without an increase in significant toxicity. These results led to the approval of trastuzumab for the treatment of advanced gastric and GEJ tumors overexpressing HER-2. In an ongoing phase III study, the role of trastuzumab in the management of earlier stage esophageal cancer is being examined as a component of multimodality

therapy with carboplatin/paclitaxel and radiation followed by surgery and adjuvant trastuzumab (Table 1). Ongoing studies are also evaluating trastuzumab in combination with chemotherapy and pertuzumab, an agent that inhibits the dimerization of HER-2 with other HER receptors, and also in combination with lapatinib and the Akt inhibitor, MK2206 (Table 2). The oral dual small molecule TKI of EGFR and HER-2, lapatinib, has also been evaluated for metastatic HER-2-positive esophageal, GEJ, or gastric cancer in the phase III LOGIC trial. This study has completed accrual, and results are awaited. Future directions for HER-2-positive esophageal and GEJ tumors may involve the novel agent, trastuzumab emtansine, which is an antibody-drug conjugate consisting of trastuzumab linked with the cytotoxic agent, mertansine. This agent, which has been remarkably well-tolerated in studies to date, has recently been approved for the treatment of HER-2 metastatic breast cancer, and a randomized phase III study is evaluating this agent versus single-agent taxane in the second-line treatment of advanced HER-2-positive GEJ and gastric adenocarcinoma (Table 2).

VEGF

VEGF is highly expressed in 28%–64% of esophageal tumors, and increased levels of VEGF correlate with more advanced stage disease and reduced survival [51, 52]. Several agents targeting VEGF have been evaluated in esophageal cancer, including mAb, bevacizumab and TKIs, sunitinib, and sorafenib. Studies of the multitargeted TKI, pazopanib; the fusion protein, ziv-aflibercept; and the receptor antibody, ramucirumab, are ongoing (Table 3). Bevacizumab is the most widely studied VEGF-targeted agent in esophageal cancer, with initially promising phase II data spurring the undertaking of a large multicenter phase III study, MAGIC-B. The investigators in this study hope to enroll 950 patients with operable disease and will examine perioperative epirubicin, cisplatin, and capecitabine chemotherapy with or without bevacizumab. In a single-arm phase II study of 47 patients with metastatic GEJ and gastric adenocarcinoma, the addition of bevacizumab to cisplatin and irinotecan chemotherapy appeared to prolong survival when compared with historical standards, reporting a median time to tumor progression of 8.3 months and OS of 12.3 months [53]. In another phase II study, the combination of bevacizumab with docetaxel, cisplatin, and fluorouracil chemotherapy led to a 67% ORR and median OS of 16.8 months [54]. Unfortunately, the AVAGAST phase III study, in which 14% of patients had GEJ primary tumors, failed to show an OS advantage for the addition of bevacizumab to chemotherapy in the first-line metastatic setting, despite demonstrating an improvement in PFS and ORR [55]. Biomarker evaluation from this study suggested that patients from non-Asian regions who had high baseline levels of VEGF-A showed a trend toward improved survival with the addition of bevacizumab, and patients with low baseline expression of neuropilin-1 also appeared to benefit from the addition of bevacizumab [56]. For patients with advanced HER-2-positive disease, a phase II study will begin shortly in which combination chemotherapy and dual targeted therapies incorporating capecitabine, oxaliplatin, bevacizumab, and trastuzumab are investigated.

Results to date with TKIs targeting VEGF have been disappointing, with significant toxicity and limited efficacy. In a

Table 2. Selected studies of EGFR- and HER-2-directed therapy in advanced esophageal cancer

Phase	NCT identifier	Patient population	Regimen(s)	Outcome or status
Cetuximab				
II	NCT00381706 (CALGB 80,403/ECOG 1206)	First-line stage IV esophageal/GEJ tumors	Epirubicin/cisplatin/fluorouracil-cetuximab, 5-FU/leucovorin/oxaliplatin plus cetuximab, irinotecan/cisplatin-cetuximab	ORR: Epirubicin/cisplatin/fluorouracil-cetuximab, 58%; 5-FU/leucovorin/oxaliplatin-cetuximab, 51%; irinotecan/cisplatin-cetuximab, 38% [60]
II	NCT00096031 (SWOG 0415)	Second-line stage IV esophageal/GEJ adenocarcinoma	Single-agent cetuximab	ORR 2%, median PFS 1.8 mo [61]
Panitumumab				
II/III	NCT00824785 (REAL-3)	First-line stage IV GEJ adenocarcinoma	Epirubicin/oxaliplatin/capecitabine plus or minus panitumumab	Terminated early; worse survival in epirubicin/oxaliplatin/capecitabine plus panitumumab arm [62]
EGFR TKIs				
II	NCT00268346	First- and second-line stage IV esophageal/GEJ tumors	Gefitinib single agent	ORR 7%, median OS 5.5 mo [63]
III	NCT01243398	Second- or third-line stage IV esophageal/GEJ tumors	Gefitinib versus placebo	OS 3.5 mo for both arms, PFS 49 d gefitinib versus 35 d placebo ($P = .01775$)
II	NCT00591123	First-line unresectable/metastatic esophageal/GEJ adenocarcinoma	5-FU/leucovorin/oxaliplatin plus erlotinib	ORR 51.5%, median PFS 5.5 mo, median OS 11 mo [64]
II	NCT00045526	Second-line unresectable/metastatic esophageal/GEJ tumors	Erlotinib single agent	ORR 7%, median OS 10.3 mo [65]
Trastuzumab				
III	NCT01041404	First-line HER-2-positive stage IV GEJ/gastric adenocarcinoma	Cisplatin/fluorouracil or cisplatin/capecitabine plus or minus trastuzumab	Median OS: Trastuzumab/chemotherapy, 13.8 mo; chemotherapy alone, 11.1 mo ($P = .0046$)
II	NCT01461057	First-line HER-2-positive unresectable/metastatic GEJ/gastric adenocarcinoma	Cisplatin/capecitabine plus trastuzumab plus or minus pertuzumab	Currently accruing
I	NCT01705340	Refractory HER-2-positive unresectable/metastatic GEJ/gastric adenocarcinoma	Trastuzumab plus lapatinib plus MK2206 (Akt inhibitor)	Currently accruing
Lapatinib				
II	NCT01145404	HER-2-positive stage IV GEJ cancer	Lapatinib plus or minus capecitabine	Currently accruing
III	NCT00680901	First-line stage IV HER-2-positive esophageal/GEJ/gastric adenocarcinoma	Capecitabine and oxaliplatin plus or minus lapatinib	Completed accrual; results pending
T-DM1				
III	NCT01641939	Second-line stage HER-2-positive GEJ and gastric cancer	T-DM1 versus taxane	Currently accruing

Abbreviations: 5-FU, 5-fluorouracil; CALGB, Cancer and Leukemia Group B; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; GEJ, gastro-esophageal junction; HER-2, human epidermal growth factor receptor-2; NCT, clinicaltrials.gov identifier; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SWOG, Southwest Oncology Group; T-DM1, trastuzumab emtansine; TKI, tyrosine kinase inhibitor.

VEGF-targeted investigations in general have been unable to identify a durable biomarker of response, and the experience with esophageal cancer illustrates this. Although signs of efficacy are seen with VEGF-targeted therapy in unselected populations, these have not been borne out in phase III randomized studies, with the exception of the 1.4-month benefit recently reported in the REGARD study.

phase II study of multimodality therapy, sunitinib was combined with CRT prior to surgery for resectable esophageal cancer, and postoperative administration of sunitinib was planned [57]. Sunitinib was poorly tolerated in the postoperative setting, and there did not appear to be a clear sign of efficacy with the preoperative combination. Similarly, in a recent phase II study, sorafenib had limited activity as a single agent for patients with pretreated metastatic esophageal and GEJ tumors; patients had a median PFS of 3.7 months and OS of 8.9 months [58].

Several studies using novel VEGF-targeted agents are ongoing, including a phase II study combining ziv-aflibercept with 5-FU/leucovorin/oxaliplatin chemotherapy for first-line

advanced disease and a phase III study of first-line 5-FU/leucovorin/oxaliplatin with or without ramucirumab. The recently reported phase III REGARD second-line study randomly assigned 355 patients in a 2:1 ratio to ramucirumab plus best supportive care (BSC) versus BSC alone [59]. Ramucirumab plus BSC demonstrated a 1.4-month survival advantage over BSC alone (5.2 months vs. 3.8 months, hazard ratio [HR] = 0.776, $p = .0473$). PFS at 3 months was 40% for ramucirumab plus BSC versus 16% for BSC alone. Overall, ramucirumab was well-tolerated. Grade 3 or greater adverse events that occurred more frequently in the ramucirumab arm were hypertension (7.6% ramucirumab vs. 2.6% BSC), hyponatremia (3.4% ramucirumab vs. 0.9% BSC), and abdominal pain (5.9% ramucirumab vs. 2.6% BSC). Given that other agents show a similar outcome when compared with BSC in this setting, choice of treatment may ultimately depend on individual oncologist and patient preference regarding side effects and cost. When reported later this year, the fully accrued RAINBOW study, which examines second-line paclitaxel chemotherapy with or without the addition of ramucirumab, should further clarify the benefit of ramucirumab for GEJ and gastric cancer.

VEGF-targeted investigations in general have been unable to identify a durable biomarker of response, and the experi-

Table 3. Selected studies of VEGF-directed therapy in esophageal cancer

Phase	NCT Identifier	Patient population	Regimen(s)	Outcome
Bevacizumab				
I/II	NCT00393068	Stage I-III resectable esophageal/GEJ tumors	Preoperative carboplatin/paclitaxel/bevacizumab Erlotinib followed by planned postoperative erlotinib/bevacizumab	Median OS 18.4 mo, 29% grade 3–4 esophagitis Postoperative erlotinib/bevacizumab not feasible [44]
II	NCT00354679	Stage IIA-IIIC resectable esophageal/GEJ adenocarcinoma	Preoperative irinotecan/cisplatin/radiation plus bevacizumab	pCR: 15%; no increase in PFS or OS [71]
II/III	NCT00450203 (ST03, MAGIC-B trial)	Stage II-IV (M1a) resectable esophageal/GEJ or gastric adenocarcinoma	Preoperative epirubicin/cisplatin/capecitabine plus or minus bevacizumab for 3 cycles followed by postoperative epirubicin/cisplatin/capecitabine plus or minus bevacizumab for 3 cycles	Currently accruing
VEGF TKI				
II	NCT00400114	Stage IIA-III resectable esophageal/GEJ tumors	Preoperative cisplatin/irinotecan/radiation followed by postoperative sunitinib 37.5 mg daily for 1 yr	Sunitinib poorly tolerated post-trimodality [56]
II	NCT00730353	First- or second-line stage IV esophageal/GEJ tumors	Weekly paclitaxel for 4 cycles plus sunitinib 37.5 mg daily for 6 cycles	ORR 11%, median OS 8 mo [72]
II	NCT00917462	First- through third-line stage IV esophageal/GEJ tumors	Sorafenib 400 mg twice a day, orally	Median PFS 3.7 mo, median OS 8.9 mo [57]
II	NCT01503372	First-line stage IV GEJ/gastric adenocarcinoma	Infusional fluorouracil plus oxaliplatin plus or minus pazopanib	Currently accruing
Other VEGF-targeted agents				
II	NCT01747551	First-line esophageal/GEJ or gastric adenocarcinoma	5-FU/leucovorin/oxaliplatin plus or minus ziv-aflibercept	Currently accruing
III	NCT01246960	First-line esophageal/GEJ or gastric adenocarcinoma	5-FU/leucovorin/oxaliplatin plus or minus ramucirumab	Completed accrual
III	NCT00917384	Second-line GEJ or gastric adenocarcinoma	BSC plus or minus ramucirumab	Median OS: ramucirumab plus BSC, 5.2 mo; BSC, 3.8 mo ($P = .04753$)
III	NCT01170663	Second-line GEJ or gastric adenocarcinoma	Paclitaxel plus or minus ramucirumab	Completed accrual

Abbreviations: 5-FU, 5-fluorouracil; BSC, best supportive care; GEJ, gastro-esophageal junction; NCT, clinicaltrials.gov identifier; ORR, overall response rate; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

ence with esophageal cancer illustrates this. Although signs of efficacy are seen with VEGF-targeted therapy in unselected populations, these have not been borne out in phase III randomized studies, with the exception of the 1.4-month benefit recently reported in the REGARD study. Efforts like the biomarker evaluation conducted in AVAGAST must continue to be prospectively incorporated into future studies with the aim of refining a predictive signature to maximize efficacy and minimize toxicity.

MET and Hepatocyte Growth Factor

Gene amplification of the MET oncogene has been reported in 2%–10% of esophageal adenocarcinoma tumors but is seen in only 1% of squamous cell cancers [66–68]. MET-amplified tumors tend to be of higher grade and present at a more advanced disease stage. In a retrospective series of 489 patients with GEJ tumors of all stages, those with MET-amplified GEJ tumors appeared to have a poor prognosis, with a median survival of 7.1 months. Survival for those with EGFR-amplified tumors was 11.2 months; for those with HER-2-amplified tumors, survival was 16.9 months; for those without amplification of MET/EGFR/HER-2, survival was 16.9 months [68]. Interestingly, two of four patients in this series with MET-amplified GEJ tumors who received the MET-targeted TKI, crizotinib, had a transient response, suggesting that MET-directed therapy may have some activity for molecularly selected patients with GEJ tumors. Tivantinib is a nonadenosine triphosphate-competitive small-molecule selective inhibitor of the receptor TK, c-Met. Tivantinib demonstrated

preliminary activity in phase I clinical studies that included patients with GEJ and gastric cancers [69, 70]. Tivantinib is currently being combined with 5-FU/leucovorin/oxaliplatin chemotherapy in a phase I/II study for molecularly unselected patients with advanced esophageal and GEJ or gastric tumors (Table 4).

In a recently published phase II study of foretinib, a multi-targeted oral TKI that inhibits c-Met, VEGFR2, AXL, TIE-2, and RON, limited activity was seen in molecularly unselected patients with advanced GEJ and gastric cancer [73]. No objective response was noted in any of the 74 enrolled patients; 43% of patients had stable disease as the best response, lasting a median of 3.2 months. Importantly, of the 67 patients in the study whose tumors were available for analysis, only 3 tumors demonstrated MET amplification.

Onartuzumab blocks hepatocyte growth factor (HGF)-mediated signaling by inhibiting MET. In an ongoing first-line phase III study, patients with advanced GEJ tumors and high levels of MET expression by immunohistochemistry are being randomly assigned to modified 5-FU/leucovorin/oxaliplatin chemotherapy with or without onartuzumab (Table 4).

Rilotumumab is a humanized anti-HGF mAb that led to prolonged PFS and a trend toward prolonged OS (11.1 months vs. 8.9 months, HR = 0.73, $p = .22$) when combined with chemotherapy in a large randomized phase II study in molecularly unselected advanced GEJ and gastric cancer [74, 75]. Of note, however, among patients with MET^{high} tu-

Table 4. Active studies of novel target or pathway-directed agents in esophageal cancer

Phase	NCT Identifier	Patient population	Agent(s)
MET/HGF			
I/II	NCT01611857	First-line stage IV molecularly unselected esophageal/GEJ/gastric adenocarcinoma	5-FU/leucovorin/oxaliplatin plus tivantinib (c-MET inhibitor)
III	NCT01662869	First-line stage IV HER-2-negative, MET-positive GEJ tumors	Modified 5-FU/leucovorin/oxaliplatin 6 plus or minus onartuzumab
III	NCT01697072	First-line stage IV MET-positive GEJ or gastric tumors	Epirubicin, cisplatin, and capecitabine plus placebo or rilotumumab
mTOR			
I	NCT01231399	Stage IV GEJ tumors	Modified 5-FU/leucovorin/oxaliplatin 6 plus everolimus
I/IIb	NCT01490749	Locally advanced esophageal tumors	Capecitabine plus oxaliplatin/carboplatin/radiation +/- everolimus
Immune-directed			
I	NCT01258868	Following resection of esophageal tumors	Adjuvant ISCOMATRIX autologous tumor vaccine and celecoxib
I	NCT01284231	Advanced gastrointestinal adenocarcinomas, including GEJ tumors	MEDI-565 (CEA/CD3 bispecific antibody T-cell activator)
I	NCT01375842	Solid tumors, including esophageal cancer	MPDL3280A (PD-L1 antibody)
II	NCT01585987	Following first-line chemotherapy for stage IV GEJ gastric tumors	Ipilimumab
PARP			
I	NCT01460888	Locally advanced esophageal/GEJ tumors	Radiation with concurrent olaparib
Hedgehog			
II	NCT00982592	First-line unresectable or metastatic GEJ/gastric adenocarcinoma	5-FU/leucovorin/oxaliplatin plus or minus vismodegib
Akt			
II	NCT01260701	Second-line stage IV GEJ/gastric adenocarcinoma	MK2206 (Akt inhibitor)
FGFR			
II	NCT01457846	Second-line stage IV FGFR-amplified esophageal/GEJ/gastric adenocarcinoma	AZD4547 (FGFR inhibitor) versus paclitaxel
Claudin-18			
	NCT01671774	CLDN18.2 expression-positive stage IV esophageal/GEJ or gastric cancer	iMAB362 (antibody targeting CLDN18.2 cell surface antigen) plus zoledronic acid
CHFR methylation			
II	NCT01372202	Locally advanced esophageal/GEJ tumors	Chemotherapy chosen based on CHFR methylation status

Abbreviations: 5-FU, 5-fluorouracil; CHFR, checkpoint with forkhead-associated and RING finger domains; EGFR, epidermal growth factor receptor; HER-2, human epidermal growth factor receptor-2; HGF, hepatocyte growth factor; FGFR, fibroblast growth factor receptor; GEJ, gastro-esophageal junction; NCT, clinicaltrials.gov identifier; OS, overall survival; pCR, pathological complete response; PD-L1, programmed death-ligand 1; PFS, progression-free survival; VEGF, vascular endothelial growth factor receptor.

mors (>50% of cells with $\geq 1+$ MET staining), OS was significantly prolonged (11.1 months vs. 5.7 months, HR = 0.29, $p = .01$), whereas there appeared to be a decrement in survival associated with the addition of rilotumumab for patients with MET^{low} tumors. Currently, a phase III trial is randomly assigning patients with advanced MET^{high} GEJ or gastric tumors to epirubicin, cisplatin, and capecitabine with rilotumumab or placebo (Table 4). Collaborative national and international efforts to conduct phase III trials in molecular subgroups of patients, such as the ongoing studies of MET-directed therapy, serve as a template for how future studies in molecularly defined subpopulations can be performed in gastroesophageal cancer.

Fibroblast Growth Factor Receptor

Fibroblast growth factor receptor (FGFR)-2 is amplified in approximately 4% of esophageal and gastric cancers and has been associated with higher tumor grade, advanced stage, and a poor prognosis [67, 76]. Preclinical data suggest that agents that inhibit FGFR-2 may have synergistic effects with chemotherapy in gastric cancer [77]. Cediranib is an oral potent inhibitor of FGFR-2, of multiple VEGF receptors, and of c-Kit. In a phase I first-line study in advanced GEJ

and gastric adenocarcinoma, cediranib 20 mg showed tolerability when combined with cisplatin/flourpyrimidine chemotherapy; however, further clinical investigation of cediranib in esophageal or gastric cancer has yet to be undertaken [78].

AZD4547 is an orally available, potent, selective inhibitor of FGFR1, FGFR2, and FGFR3 and is currently being compared with second-line chemotherapy for FGFR-amplified advanced esophageal, GEJ, or gastric cancer in a randomized phase II study (Table 4) [38]. Given experiences with other pathway-specific agents in diverse tumors, this strategy of molecular selection appears wise and the one most likely to yield clinically relevant benefits.

Novel Directions

Several other cellular pathways, targets, and molecular strategies are undergoing clinical investigation for esophageal or GEJ cancer (Table 4). The potential synergy of radiation and poly(adenosine diphosphate-ribose) polymerase inhibition is being explored in a phase I trial for locally advanced esophageal and GEJ tumors. Immune-based therapies are also entering clinical investigation, including the anticytotoxic T-lymphocyte antigen-4 immune checkpoint anti-

body, ipilimumab, for advanced disease and adjuvant vaccine-based strategies after surgical resection. Next-generation immune checkpoint antibodies, including anti-programmed death-1 antibody and anti-programmed death-ligand-1 are undergoing investigation in solid tumors that include esophageal cancer. At our own institution, we have opened a phase II epigenetic biomarker study examining the impact on pCR rate of choosing concurrent systemic therapy for locally advanced esophageal cancer based on the methylation status of checkpoint with forkhead-associated and RING finger domains (CHFR). We are also exploring whether CHFR methylation status predicts improved response to modified docetaxel, cisplatin, and 5-FU as first-line therapy in metastatic disease.

CONCLUSION

Anti-HER-2 therapy has efficacy for the 10%–15% of patients with upper GI tumors that overexpress HER-2; however, for most patients with esophageal cancer, targeted therapies have been unsuccessful to date. Genomic sequencing of esophageal tumors has revealed few driver mutations to rival those seen in non-small cell lung cancer, although the relatively frequent occurrence of gene amplifications and their association with aggressive disease will guide investigation of targeted agents in molecularly selected patients. The VEGFR2 antibody, ramucirumab, has recently demonstrated activity for second-line therapy in patients with advanced GEJ and gastric cancer when compared with placebo. We await the results of the first-line phase III study of this agent. Development of biomarkers of re-

sponse to VEGF-targeted agents has been stubbornly difficult, although recent data from the AVAGAST study are encouraging in this regard. Several phase III MET inhibitor studies are ongoing, and given encouraging phase II results in those with MET^{high} disease, it is hoped that these agents may demonstrate efficacy and bring additional options to the clinic. Future phase III investigation of targeted agents should be conducted among collaborative groups, where accrual of relatively uncommon molecular subgroups is most likely to be successful. Novel strategies including immunotherapy are also of interest, particularly in view of recent successes in other seemingly nonimmunogenic tumors.

AUTHOR CONTRIBUTIONS

Conception/Design: Patrick M. Forde, Ronan J. Kelly

Provision of study material or patients: None

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Data analysis and interpretation: Patrick M. Forde, Ronan J. Kelly

Manuscript writing: Patrick M. Forde, Ronan J. Kelly

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