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ESOPHAGEAL ADENOCARCINOMA: TREATMENT MODALITIES IN THE ERA OF TARGETED THERAPY

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Abstract

Esophageal adenocarcinoma is an aggressive malignancy with a poor outcome, and its incidence continues to rise at alarming rates. Current treatment strategies combining chemotherapy, radiation, and surgery are plagued with high rates of recurrence and metastasis. Multiple molecular pathways including the epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), v-erb-b2 erythroblastic leukemia viral oncogene homolog (ERBB2), and Aurora kinases' (AURK) pathways are activated in many esophageal adenocarcinomas. In many cases, these pathways have critical roles in tumor progression. Research on the mechanisms by which these pathways contribute to disease progression has resulted in numerous biologic agents and small molecules with the potential to improve outcome. The promise of targeted therapy and personalized medicine in improving the clinical outcome is now closer than it has ever been.

THE SCOPE OF THE CLINICAL PROBLEM

Although squamous cell carcinomas predominate worldwide, 70% of esophageal cancers in the United States are adenocarcinomas [1]. In fact, the incidence of esophageal adenocarcinoma (EAC) continues to rise in the Western world [2,3]. In the United States, 16,470 cases of esophageal cancer, with the majority being adenocarcinomas, were diagnosed in 2008 with 14,280 deaths. In addition, there is an increasing incidence of gastroesophageal junction (GEJ) adenocarcinomas in the United States. The recent surge in these tumors is attributed to the increase in gastroesophageal reflux disease [4–6]. EAC is a unique disease process that is etiologically and genetically distinct from other gastrointestinal malignancies such as gastric adenocarcinoma [7]. Genetic and epigenetic alterations are common in EACs and promoter DNA hypermethylation of several antioxidant and DNA repair genes has been described [8–12]. Although most patients present with advanced disease, the minority of patients presenting with localized disease can be treated with surgery alone, surgery combined with chemotherapy, chemoradiation alone, or preoperative chemoradiation followed by surgery [13–15]. Some

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meta-analyses have suggested that trimodality therapy is superior to surgery alone and that patients with a complete pathologic response prior to surgical resection have better outcomes than other patients [16–18].

SURGICAL THERAPY AND ITS LIMITATIONS

A fundamental factor in determining the surgical options is the location of the tumor. In general, esophagectomy is performed, but resection for GEJ tumors also involves a partial or complete gastrectomy [19]. When possible, the stomach is the preferred esophageal replacement due to vascularity and ease of use, although colon can also be utilized with good results [20]. Five-year survival rates following surgery are reported to be from 10–40%, although selected patients at high-volume centers have 5-year survival rates exceeding 60% [21–24]. Patients with five or more positive lymph nodes have a lower 5-year survival than those with node negative disease (10.7% vs. 22.5%) [23–25]. Surgical approaches have numerous limitations, including higher mortality in individuals with comorbidities or poor performance status [26]. Esophagectomy has numerous possible complications, including myocardial infarction, pneumonia and respiratory failure, wound infection, postoperative ileus, bowel obstruction, and anastomotic leak [27]; the use of a stapled cervical anastomosis reduces the combination of leak and stricture (3% vs. 13%) for transhiatal esophagectomy [28]. The location of the anastomosis (intrathoracic versus cervical) does not affect the leak rate, but intrathoracic leaks are more morbid due to the resulting mediastinitis [28].

Few trials have compared transhiatal, transthoracic, and en-bloc esophagectomy. These trials, including one randomized trial, have not shown a difference between transhiatal and transthoracic techniques, although there is evidence that better results are obtained at high-volume centers [21,29,30]; there is non-randomized evidence that en-bloc esophagectomy may provide better survival and recurrence rates than transhiatal esophagectomy [31]. The risk of metastasis, predominantly driven by lymphatic spread, dramatically increases with depth of invasion [32–34]. Without additional therapy, surgery alone has a significant rate of local recurrence, perhaps as high as 35% [35]. Investigators began to study the use of other modalities, such as chemotherapy, radiotherapy, and combinations thereof, to improve outcome.

CHEMOTHERAPY AND RADIOTHERAPY

The use of perioperative chemotherapy has shown an improvement in survival in phase III randomized studies. Patients enrolled in the MAGIC trial (n=503, 75% gastric adenocarcinoma and 25% esophageal and GEJ tumors) were randomized to perioperative epirubicin, cisplatin and 5-fluorouracil with a significant improvement in 5-year survival rate (36% vs. 23%) but no improvement for purely adjuvant chemotherapy [36]. A large trial with 802 patients randomized to surgery alone or surgery plus two neoadjuvant cycles of cisplatin/5-FU did show a survival benefit with neoadjuvant chemotherapy, although that benefit was largely diluted at 5 years (23% vs. 17%) [37]. However, another trial indicated that neoadjuvant chemotherapy did not improve the rate of tumor recurrence in esophageal adenocarcinoma [38].

Radiation therapy alone is used for palliation, with 5-year survival rates of 0–10%; it yields lower survival rates than concurrent chemoradiation and has a locoregional recurrence rate of 50% [39]. Studies have not demonstrated a survival benefit to the addition of neoadjuvant radiotherapy without concurrent chemotherapy, with 5-year survival ranging from 10–37% for preoperative radiotherapy versus 9–33% for surgery alone [40–44].

Phase II studies have shown that neoadjuvant chemoradiotherapy followed by surgery significantly reduces 3-year mortality and locoregional recurrence [16]. There are a number of regimens including cisplatin and 5-fluoropyrimidine, irinotecan and cisplatin, paclitaxel and

cisplatin or carboplatin, docetaxel and cisplatin or a taxane with fluoropyrimidine [14,45]. Radiation, when used in combination with chemotherapy usually consists of 4500–5040 centigray given in 25 to 28 fractions, over 5 to 5–1/2 weeks [46,47]. However, the role of neoadjuvant chemoradiotherapy in the management of localized esophageal cancer remains controversial. Meta-analyses have shown superior outcomes for trimodality therapy; one study reported a hazard ratio of 0.81 for all-cause survival ($P=0.002$) [48] and a second demonstrated both a survival benefit and reduced local recurrence rate [49]. A third meta-analysis found a trend toward improved survival that did not approach statistical significance (HR 0.88 [95% CI 0.75–1.04]) [50]. In addition, patients receiving neoadjuvant chemotherapy may experience higher perioperative mortality [17]. Although the survival benefit to trimodality therapy is still controversial, the benefit to local control may be significant. Local recurrence rates of 15% have been reported for trimodality therapy [38], and this effect has been replicated in one meta-analysis [49] although a second returned a negative result [50]. Neoadjuvant therapy has the added benefit of being able to downstage the tumor [51] and use pathologic response rates as an early surrogate marker of efficacy in the development of new drugs and new combined modality regimens. Currently, 5-year survival is 100% for stage 0 (*in situ* disease), 79% for stage I (tumor within the submucosa), 38% for stage IIA (tumor within the muscularis propria or invading paraesophageal tissue but not adjacent structures), 27% for stage IIB (tumor within the muscularis propria with regional lymph node metastases), 14% for stage III (invasion of paraesophageal tissue or adjacent structures with regional lymph node metastases), and 0% for stage IV (distant metastases) [52]. A large majority of patients present with Stage III or IV disease. There is clearly a great deal of room for improvement in the treatment of cancers of the esophagus. Targeted therapies offer a potential avenue of improvement over current therapeutic regimens.

THE PERSPECTIVE OF TARGETED THERAPY

Molecular-targeted therapy, designed rationally to inhibit appropriate signaling pathways in human solid tumor, may provide effective, highly selective, and well-tolerated anticancer treatments. Several recent reports suggest that cancer cells' survival becomes dependent on the expression of a critical pro-survival protein [53]. Despite the complexity of cancer cells, their growth and survival can often be impaired by the inactivation of a single oncogene [53, 54]. This phenomenon, called “oncogene addiction,” provides a rationale for molecular targeted therapy [54,55]. In fact, this is the driving foundation for gene targeted therapy approaches in cancer such as trastuzumab (Herceptin) and imatinib (Gleevec) agents that block the specific cancer-cell-dependent signaling pathways. Combination therapy may also be required to prevent the escape of cancers from a given state of oncogene addiction [53,56]. Experimental evidence surprisingly illustrates that the inactivation of even a single oncogene can be sufficient to induce sustained tumor regression. The proposed explanation for this phenomenon is that activated oncogenes result in a signaling state in which the sudden abatement of oncogene activity balances towards proliferative arrest and apoptosis [57]. Understanding when and how oncogene inactivation induces apoptosis is important when developing effective strategies for the treatment of cancer [55]. In the following sections we will briefly review some potential targeted therapy approaches in EAC.

Epidermal Growth Factor Pathway Inhibitors

The epidermal growth factor receptor (EGFR) as well as its ligands, EGF and transforming growth factor α (TGF- α), have been implicated in cell proliferation, cell survival, angiogenesis, and metastasis [58] (Figure 1). EGFR is upregulated in high-grade dysplasia [59] and overexpressed by a factor of four in esophageal adenocarcinoma [60], particularly in poorly differentiated tumors [61]. Increased expression of TGF- β and the EGF receptor have been detected in EAC [62,63]. EGFR upregulation is a poor prognostic factor in esophageal

adenocarcinoma and has been associated with lymph node metastases, higher TNM staging, and decreased overall and recurrence-free survival [64,65]; increased EGFR immunoreactivity has also been correlated with decreased overall survival [66].

EGFR is a key mediator in the progression from normal esophageal tissue to Barrett's esophagus and finally to esophageal adenocarcinoma. Intestinal metaplasia has been shown to depend on the upregulation of caudal homeobox 2 (CDX2) [67–69]. Deoxycholic acid, a major component of human bile, results in ligand-dependent EGFR activation and CDX2 induction, even in the absence of acidic pH [70]. Thus, EGFR is implicated in the progression to Barrett's esophagus, a key step in esophageal carcinogenesis. Activating EGFR mutations in exons 18 and 21, first found in non-small cell lung cancers, have also been identified in a subset of patients with Barrett's esophagus, high-grade dysplasia, and esophageal adenocarcinoma [71]. Decrease in EGFR mRNA expression in surgical specimens compared to pre-treatment endoscopic specimens has been associated with the degree of tumor regression [72]. Given the significant implication of EGFR in multiple steps of the progression toward esophageal adenocarcinoma, it is not surprising that EGFR and its associated pathways have become an active area of investigation for targeted therapeutics in esophageal adenocarcinoma. Several EGF receptor pathway inhibitors continue to enter clinical trials for esophageal and GEJ adenocarcinomas (Table 1). Among monoclonal antibodies that inhibit EGFR through high-affinity binding, cetuximab and panitumumab are already approved in the United States for advanced colorectal cancer [73]. Cetuximab is also used for advanced head and neck squamous cell carcinoma and has an acceptable side effect profile when given in conjunction with paclitaxel, carboplatin, and radiation [74]. A phase II trial of cetuximab in conjunction with the standard FOLFIRI regimen in a cohort of 38 predominantly metastatic patients showed an overall response rate of 44.1% (95% CI 27.5–60.9%). Median time to progression was eight months (95% CI 7–9 months) and median survival was 16 months (95% CI 9–23 months) [75]. Neoadjuvant panitumumab in conjunction with docetaxel, cisplatin, radiation, and surgery is currently being studied in the treatment of patients with locally advanced esophageal or GEJ tumors (ACOSOG Z4051, <https://www.acosog.org>).

Small molecule tyrosine kinase inhibitors competitively bind the ATP binding site of the EGF receptor, preventing it from successfully activating even with bound ligand. This group contains gefitinib, erlotinib, and lapatinib [76]. After being shown to arrest growth of esophageal cancer cell lines in culture [77], erlotinib progressed to phase I and II clinical trials and was shown to be safe in conjunction with cisplatin, 5-FU, and radiotherapy [78]. A phase II trial of erlotinib in patients with unresectable or metastatic gastric or GEJ adenocarcinoma indicated a 9% (95% CI 3–22%) response rate for GEJ tumors, although there was no response in patients with gastric adenocarcinomas [79]. Gefitinib with oxaliplatin and radiotherapy for patients with either metastatic or locally advanced but unresectable esophageal adenocarcinoma achieved complete mucosal response, partial response, and absence of progression in one case each, although no change in the level of EGFR was noted after treatment in this study [80]. These results seem somewhat poorer than those reported from a phase II study of gefitinib monotherapy in patients with advanced inoperable esophageal adenocarcinoma. In this study of 27 patients, three patients had a partial response and seven had stable disease, for an overall disease control rate of 37% [81].

Trials of EGFR inhibitors thus far have been less promising than hoped. It is possible that the subset of patients who would benefit from EGFR inhibitors have not been properly identified; the presence of EGFR in a tumor may not be sufficient to ensure response to EGFR inhibitors. In addition, K-RAS mutations, which predict for EGFR inhibitor resistance [82,83], are found in almost one-third of esophageal adenocarcinomas [84]. Additional trials, perhaps incorporating multiple axes of EGFR inhibition or inhibition of K-RAS and EGFR, may have a better response. One of these trials, NCT00397384 (<http://www.clinicaltrials.gov>), involves

cetuximab and erlotinib in a phase I/II study of multiple types of carcinoma. If successful, this trial could spawn additional trials focused on multiple axes of EGFR inhibition.

Vascular Endothelial Growth Factor Pathway Inhibitors

One notable subset of the EGFR receptor pathway is the ligand-receptor relationship between VEGF and the VEGF receptor. In one study deoxycholic acid was associated with upregulation of VEGF in the OE33 Barrett's adenocarcinoma cell line, indicating that bile reflux may have the potential to induce increased angiogenesis via the VEGF pathway [85]. VEGF has also been shown to be upregulated sequentially at the mRNA level along the metaplasia-dysplasia-adenocarcinoma sequence, although EGFR mRNA was not upregulated [86]. VEGF-A, associated with angiogenesis, and lymphangiogenesis-associated VEGF-C were found to be co-expressed with COX-1 and COX-2, and *in vitro* inhibition of the COX pathways also inhibited expression of VEGF isoforms. Specific polymorphisms in VEGF were associated with an increased odds ratio for esophageal adenocarcinoma via logistic regression among a cohort of patients with esophageal adenocarcinoma and healthy controls. A subset of these VEGF haplotypes modified the effect of smoking history on the odds ratio of esophageal adenocarcinoma as well, indicating that some compounds in cigarette smoke might potentially interact with specific VEGF haplotypes in a fashion that encourages angiogenesis through VEGF pathway activation [87]. Although VEGF may be associated with tumor initiation, it was associated with intestinal-type rather than diffuse type gastric adenocarcinoma in a combined study of gastric and esophageal adenocarcinoma samples, and it did not predict a poor prognosis [88]. One multicenter phase II trial of bevacizumab (VEGF inhibitor) in conjunction with irinotecan and cisplatin in patients with stage IV gastric or GEJ adenocarcinoma indicated an improvement in time to disease progression and overall survival when compared to historical controls [89]; clearly more study is warranted. Multiple additional compounds that target VEGFR-1 expression, block VEGFR-2, or inhibit the tyrosine kinase activity of various VEGF receptor types are under preclinical investigation (Table 1) [90]. It is possible that some of these agents may show promise in esophageal adenocarcinoma, providing an avenue to target tumor angiogenesis.

ERBB2/HER-2 Inhibitors

The HER-2 receptor, a member of the EGFR family (Figure 1) located at the 17q amplicon, has also been implicated in carcinogenesis and metastasis [76]. A 200 kbp segment in the vicinity of the HER-2 gene, including DARPP-32 and human growth factor receptor-bound protein 7 (GRB7), is amplified in a subset of esophageal adenocarcinoma [91–93]. Mechanistically, HER-2 constitutively activates and upregulates MAP kinase and Phosphoinositide-3 kinase (PI3K) pathways. These pro-survival signaling pathways, in turn, abrogate apoptosis and cause cell cycle progression [92]. Although HER-2 was initially studied due to its overexpression in 25% of breast adenocarcinomas, it is also amplified and/or overexpressed in esophageal adenocarcinomas and their metastases [91,94–97]. Decrease in HER-2 mRNA expression in surgical specimens, as compared to pretreatment endoscopic specimens, has also been associated with the degree of tumor regression [72]. These studies, although not conclusive, lend credence to the theory that the humanized monoclonal anti-HER-2 antibody trastuzumab might be effective in HER-2-expressing esophageal adenocarcinomas. The co-amplification of the other genes in the 17q amplicon in conjunction with HER-2 is concerning, particularly DARPP-32 and its truncated cancer-specific isoform t-DARPP [98,99]. This is of a particular importance since t-DARPP has been shown to activate the AKT survival signaling pathway and mediate trastuzumab resistance in breast cancer [100,101]. Trastuzumab treatment of HER-2-expressing esophageal adenocarcinoma cell lines with and without concomitant radiation showed that the two treatments were synergistic, although 10 mcg/mL trastuzumab alone was insufficient to induce cell death [102]. A recent phase I/II study of trastuzumab with cisplatin and paclitaxel in locally advanced esophageal

adenocarcinomas strongly expressing HER-2 by immunohistochemistry showed a median survival of 24 months [103], indicating a possible role for HER-2 inhibition. Two additional phase I trials of trastuzumab in conjunction with tipifarnib and interleukin-12 have recently been completed and results are pending (Table 1). In addition, the recently completed ToGA trial of trastuzumab added to standard chemotherapy in HER-2-positive advanced gastric adenocarcinoma demonstrated improved overall and progression-free survival; thus, there is a possibility that the same agent would be helpful for HER-2 positive esophageal adenocarcinoma. [104,105].

Aurora Kinase Inhibitors

The three mammalian Aurora kinases are members of the serine-threonine protein kinase family. Their expression is regulated by the cell cycle; Aurora kinases A (AURKA) and B (AURKB) are expressed in G2, while Aurora kinase C (AURKC) is mostly expressed in meiosis [106,107]. AURKA assists in mitotic spindle creation by helping to regulate centrosome duplication and separation; it is also involved in microtubule-kinetochore attachment and cytokinesis [108,109] (Figure 2). AURKA overexpression amplifies the centrosome and causes cytokinetic failure with concomitant aneuploidy [110]. AURKB has been associated with chromosomal condensation, mitotic spindle assembly, and cytokinesis, while AURKC has been implicated in karyotype stability during meiosis in mouse models [106]. Most of the recent studies implicate AURKA and AURKB in cancer development and progression. AURKA is overexpressed in many human primary tumors and premalignant conditions and can contribute to aggressive disease. In particular, AURKA is frequently overexpressed in EAC and GEJ adenocarcinomas [111]. AURKA polymorphisms, not studied in EAC, have been associated with elevated breast cancer risk [112] and earlier onset of pancreatic adenocarcinoma [113]. Recent studies have shown that overexpression of AURKA mediates potent pro-survival properties in cancer cells through activation of the AKT pathway and inhibition of p53- and p73-dependent apoptosis [111,114]. Furthermore, AURKA expression results in GSK-3 β phosphorylation, in turn resulting in decreased β -catenin phosphorylation and accumulation and activation of the oncogenic β -catenin/TCF transcription complex [115]. Thus, the importance of the Aurora kinases in regulation of the cell cycle, apoptosis, and p53/TAp73 activity has encouraged the investigation into Aurora kinase inhibition as a mode of targeted therapy. A variety of Aurora kinase inhibitors have been developed and some have been evaluated in clinical studies (Table 1). MK-0547 has been effective in xenograft models of ovarian cancer [116]. The Aurora kinase inhibitor VE-465 has anticancer effects in pre-clinical studies of human hepatocellular carcinoma [117]. Thus far, neutropenia and somnolence have emerged as dose-limiting toxicities in at least two separate trials, and hypertension and diarrhea have been observed [118,119]. Aurora kinases continue to be attractive targets for drug development and clinical studies. Because of the expression of Aurora kinases in esophageal adenocarcinomas, aurora kinase inhibitors represent a possible opportunity for investigation and may provide an alternate modality for targeted chemotherapy.

CONCLUDING REMARKS

Many strides have been made in the treatment of esophageal adenocarcinoma, an aggressive malignancy with poor outcomes even with the best known therapies. Further improvements for patients with this malignancy are likely to result from research on novel pathways. When a better understanding of the mechanisms of pathogenesis and tumor progression in esophageal adenocarcinoma is achieved, it will be easier to proceed with targeted therapies that focus on an individual's specific tumor biology and molecular signature. A great deal of work still needs to be done in elucidating the mechanisms involved in the progression from normal esophageal tissue to esophageal adenocarcinoma. The better we understand the basic pathways involved in the development and growth of cancers of the esophagus; we can anticipate that additional

therapeutic modalities will present themselves, providing patients with the hope for an improved outcome.

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Figure 1.

The EGF receptor family is a group of receptor tyrosine kinase receptors that result in activation of the JAK/STAT, RAS/RAF, and PKC pathways. Bevacizumab is a VEGF inhibitor. Cetuximab, matuzumab, and panitumumab inhibit the EGF receptor at the ligand binding site, while trastuzumab inhibits the HER-2 receptor via the same mechanism. Erlotinib, gefitinb, and lapatinib inhibit the tyrosine kinase moiety for the EGF receptor, while vandetanib and brivanib have the same mechanism of inhibition for the VEGFR-2 receptor. Sunitinib inhibits the tyrosine kinase moiety for the VEGF and PDGF receptors. Sorafenib is a selective RAF kinase inhibitor.

Figure 2.

Aurora kinase A and B both play a role in centromere and kinetochore formation. Aurora kinase B also has a role in microtubule and bipolar spindle formation and cytokinesis. On a molecular level, Aurora kinase A acts to inhibit p53 and p73, as well as phosphorylation of GSK-3 β , resulting in dephosphorylation and accumulation of β -catenin. MLN-8237 is a selective Aurora kinase A inhibitor, while AT-9283, PF-03814735, and SNS-314 inhibit both Aurora kinase A and B. YC-116 inhibits both Aurora kinases and VEGFR-2, while AMG-900 inhibits Aurora kinase A, B, and C.

Table 1

Clinical Trials Involving Targeted Therapeutic Agents

Drug Class	Drug	Other drugs*	Surgery	Radiation	Phase	Patient Population**	Patients	NCT ID	Status
EGFR Inhibitor	Cetuximab	cap, ox	yes	yes	N/A	E (adv)	15	430027	recruiting
		cis, epi, 5-FU/ leuc, iri, ox	yes	yes	II	E	30	827671	recruiting
			no	no	II	E, GEJ (met)	270	381706	recruiting
		cix, iri	no	no	II	E, G, GEJ (met)	25	397904	recruiting
		pac	no	yes	III	E	420	655876	recruiting
			no	no	II	E, GEJ (met)	55	96031	active, not recruiting
		cis, 5-FU	yes	yes	I/II	E	45	544362	recruiting
		cis, doc	yes	yes	I/II	E (adv)	27	445861	active, not recruiting
		cis, iri	no	yes	II	E (adv)	100	109850	active, not recruiting
		cap, cis	no	yes	II/III	E	420	509561	recruiting
EGFR Inhibitor/TK Inhibitor	Matuzumab	ECX	no	no	I	E, G	26	113581	completed
		ECX	no	no	II	E, G	72	215644	completed
	Panitumumab	iri	no	no	II	E	43	836277	not recruiting
		EOX	yes	no	I/II	E, G	30	667420	recruiting
		cis, doc	yes	yes	II	E, GEJ (adv)	69	757172	recruiting
			no	no	I	E, GEJ, RCC, PC, PANC, NSCLC, CRC	15	4879	active, not recruiting
	Cetuximab/Erlotinib		no	no	I/II	E, HN, NSCLC, CRC	55	397384	recruiting
	Trastuzumab	tipifamib	no	no	I	E, G (adv, rec, met)		5842	completed
		Interleukin-12	no	no	I	E, G (adv, rec, met)	15	4074	completed
	Erlotinib	FOLFOX	no	no	II	E, G (unr, met)	38	591123	recruiting
			no	no	II	E, GEJ (adv, met)		32123	completed
			no	no	II	G, E		45526	completed
			no	yes	II	E (stage I-IV, older patients)	35	524121	recruiting
EGFR TK Inhibitor	Gefitinib	preop: cis, pac	yes	yes	II	E, GEJ (adv)	36	493025	recruiting

Drug Class	Drug	Other drugs*	Surgery	Radiation	Phase	Patient Population**	Patients	NCT ID	Status
		ox cis, 5-FU cis, iri	no	yes	I/II	E (adv, met)	80	93652	active, not recruiting
			yes	yes	II	E, GEJ (adv)	20	258323	active, not recruiting
			yes	yes	I/II	E, GEJ	72	290719	active, not recruiting
			no	no	II	E (adv)	76	100945	active, not recruiting
			no	no	II	E, GEJ (met, rec)	76	268346	recruiting
	Lapatinib		no	no	II	E (rec)	24	259987	completed
			no	no	III	E, G, GEJ (adv, met, rec)	410	680901	recruiting
			no	no	II	E, GEJ (met)	98	891878	not recruiting
			no	no	I	G, E (adv)	30	524186	recruiting
			no	no	II	G (met)	50	411151	active, not recruiting
RTK Inhibitor	Sunitinib	cap iri, 5-FU/leuk	no	no	II	E, GEJ (met)	98	891878	not recruiting
			no	no	I	G, E (adv)	30	524186	recruiting
			no	no	II	G (met)	50	411151	active, not recruiting
RAFK Inhibitor	Sorafenib		no	no	II	E, GEJ (met, rec)	35	917462	recruiting
VEGF Inhibitor	Bevacizumab	doc, cis, 5-FU	no	no	II	E, G (unr, met)	44	390416	active, not recruiting
		cap, cis, doc, epi, iri	yes	no	II	G, GEJ (adv)	60	737438	recruiting
		doc, ox	no	no	II	G, GEJ (adv, unr, met)	38	217581	recruiting
		erlotinib	no	no	II	gallbladder, cholangiocarcinoma	126	350753	completed
		iri, cis	no	no	II	G, GEJ	47	354679	completed
		cap, cis, epi	yes	no	II/III	G, GEJ	1100	450203	recruiting
VEGFR-2 Inhibitor	Brivanib	plc	no	no	II	G, E, NSCLC, BL, SARC, PANC	300	633789	recruiting
	Vandetanib	doc, ox	no	no	I/II	E, GEJ (adv)	92	732745	active, not recruiting
Bcl-2 antisense oligo	Oblimersen	cis, 5-FU	no	no	I/II	E, G, GEJ (adv)		64259	active, not recruiting
			no	no	I/II	E, BL, BC, CRC, HN, RCC, LC, O			
HDAC Inhibitor	Vorinostat	iri, 5-FU/leuk	no	no	I	G, E, HCC	25	537121	recruiting
Aurora Kinase A Inhibitor	MLN8237		no	no	I	Adv Solid Tumors	60	500903	recruiting
			no	no	I	Adv Solid Tumors	44	651664	recruiting
Aurora Kinase A/B Inhibitor	AT9283		no	no	I	Adv/Met Solid Tumors	30	443976	recruiting

Drug Class	Drug	Other drugs*	Surgery	Radiation	Phase	Patient Population**	Patients	NCT ID	Status
	PF03814735		no	no	I	Adv Solid Tumors	60	424632	recruiting

* Other drugs: **cap**, capecitabine; **cis**, cisplatin; **doc**, docetaxel; **ECX**, epirubicin, cisplatin, capecitabine; **EOX**, epirubicin, oxaliplatin, capecitabine; **FOLFOX**, 5-FU, leucovorin, oxaliplatin; **iri**, irinotecan; **ox**, oxaliplatin; **pac**, paclitaxel; **plc**, placebo

** Patient population: **BC**, breast adenocarcinoma; **BL**, bladder cancer; **CRC**, colorectal cancer; **E**, esophageal cancer; **G**, gastric cancer; **GEJ**, gastroesophageal junctional cancer; **HCC**, hepatocellular carcinoma; **HN**, Head and neck cancer; **LC**, lung cancer; **NSCLC**, Non-small cell lung cancer; **Ov**, **ovarian cancer**; **PANC**, pancreatic adenocarcinoma; **PC**, Prostate adenocarcinoma; **RCC**, Renal cell carcinoma; **SARC**, soft tissue sarcoma; **U**, uterine; **adv**, locally advanced; **met**, metastatic; **rec**, recurrent; **unr**, unresectable