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Esophageal Cancer: Current and Evolving Treatment Landscape

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Abstract

With advances in state-of-the-art technology, trendy diagnostic and prognostic molecular markers, and cutting-edge surgical techniques, the overall survival for patients with many types of cancers has improved. However, there is a disconnect between esophageal cancer and the acceleration in cancer care seen in other malignancies. Based on data reported by Surveillance, Epidemiology, and End Results Program (SEER), the 5-year survival rate for patients with esophageal cancer is only 19.9% [1]. Poor prognosis is likely due to an overwhelming number of patients with advanced disease during the time of diagnosis, and is also reflective of the unsatisfactory outcomes from current treatments.

In this article, we will review the epidemiology and the recently revised staging of esophageal and esophagogastric junction cancers. We will discuss the current roles of endoscopic resection, surgery, radiation therapy, and systemic therapy used individually, or as components of multimodality treatment. We will describe the changes in treatment landscape with targeted therapy and immunotherapy. The focus of clinical investigations continues to shift from the traditional empiric chemotherapy to more individualized treatments based on molecular oncology and use of immunotherapy. Further identification of prognostic values may help clarify the optimal approach to treatment and management for patients with esophageal cancer, and hopefully improve survival.

Introduction

Esophageal cancer poses a significant health risk as the 8th most common cancer worldwide, owning close to 456,000 new cases and 400,000 deaths each year [2]. The majority of esophageal cancers fall into two histologic subtypes, Esophageal Squamous Cell Carcinoma (ESCC) and Adenocarcinoma of the Esophagus (EAC). These are separated by well-recognized differences in global distribution, racial predilection, risk factors, molecular pathogenesis, and anatomic distribution [3]. Controversy exists, however, as to the variations in biological behavior, patterns of spread, response to therapy, and proper approach to treatment. Historically, the majority of cancers of esophageal origin were classified as ESCC. While still true, the epidemiology shifted dramatically between 1960 and 1990, favoring higher incidence rates of EAC and declining rates of ESCC in both previously ESCC-dominant countries and white male populations of higher income countries [4]. New reports suggest that by 2030, over 1 in 100 men in the UK will develop EAC before the age of 75. The exact etiology of this gradient in EAC towards high income countries is still unknown, but may be attributed to higher obesity rates and genetic predisposition, while the decreased incidence of ESCC may be reflective of the decline in smoking.

In an effort to improve the classification of esophageal cancer beyond histopathologic and epidemiologic characteristics, to better understand the demarcation between esophageal and gastric cancers, and to discover potential targets for therapy, The Cancer Genome Atlas Research Network (TCGA) performed a comprehensive molecular analysis of 559 esophageal and gastric cancer samples from patients around the world [5]. Frequent findings in ESCC included genomic amplifications of CCND1 and SOX2 and/or TP63. In contrast, tumors of adenocarcinoma histology consisted of amplifications in ERBB2, VEGFA, GATA4,

and GATA6. In addition, the EAC tumors strongly resembled chromosomally unstable variants of gastric adenocarcinoma. These findings supported the notion that cancers of the upper esophagus more closely resemble head and neck cancers, and cancers of the lower esophagus are almost indistinguishable from cancers of the stomach with chromosomal instability. The recently reported molecular signatures and antidotal discrepancies in response to therapy between ESCC and EAC validate the decision to separate these two disease entities when staging and determining overall prognosis, particularly in conducting clinical trials.

Staging

The Tumor Node Metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) is used universally and is critical for guiding treatment and determining prognosis. In the seventh edition of AJCC staging, prognostication for esophageal cancer is based on pathologic findings obtained after surgery alone. To determine the utility of the seventh edition, the Worldwide Esophageal Cancer Collaboration (WECC) analyzed a series of patient and cancer characteristics from 33 institutions in 6 continents [6,7]. The group generated the following conclusions: First, the seventh edition clinical staging system is unreliable and inaccurate, as it is primarily based on imaging without significant considerations of histologic and biomarker information. Second, the pathologic staging based on esophagectomy alone is relevant to early-stage disease, but not to advanced esophageal cancers. And lastly, taking into account for both the effects of neoadjuvant treatment and esophagectomy on tumor depth, nodal status, and metastasis, is better informative of prognosis than using factors based on esophagectomy alone. Based on these findings, the eighth edition of AJCC staging manual now includes major changes in staging epithelial cancers of the esophagus and Esophagogastric Junction (EGJ). Cancers of the esophagus and EGJ are now classified separately. ESCC and EAC have individual staging classifications as well. Tumors are now classified into clinical (cTNM), pathologic (pTNM), and postneoadjuvant pathologic (ypTNM) groups, which include non-anatomic categories, grade (G) for both histologic types and location (L) for squamous cell cancer. The definition of tumor location has also been changed for esophageal cancer from the position of the lower edge of the cancer to the epicenter, determined from the upper and lower border measurements. If the epicenter of a tumor is 2 cm or less from the gastric cardia, it is considered EAC. Those that are more than 2 cm into the gastric cardia are staged as gastric adenocarcinoma. This is a change from the seventh edition AJCC staging, in which tumors arising at the EGJ or at the gastric cardia within 5 cm of the EGJ are classified as esophageal cancer rather than gastric. The revisions contained in the eighth edition of the AJCC staging manual took effect on January 1, 2018.

Approach to Treatment

Surgery remains the cornerstone of treatment for localized disease in patients who are considered medically fit for surgery. Emerging data suggest patients with early esophageal cancer limited to the lamina propria or muscularis mucosa may be effectively treated with endoscopic resection. Multimodality treatment with neoadjuvant chemotherapy and Radiation Therapy (RT) followed by surgery is generally indicated for tumors invading the submucosa and beyond without invasion of adjacent structures, and/or those with lymph node involvement. For patients with locally advanced and metastatic disease, the goal of treatment is often palliative. Palliation may be achieved by systemic treatment (chemotherapy, targeted therapy, and immunotherapy) and local modalities such as RT and endoscopic interventions. Supportive measures include efforts to relieve esophageal obstruction, to establish adequate nutrition and pain control, and to manage blood loss. In addition to the approved treatment options, the National Comprehensive Cancer Network (NCCN) highly recommends participation in all phases of clinical trials.

Endoscopy & Surgery

Endoscopic Resection (ER) allows for precise assessment of tumor depth and complete eradication of early-stage disease (including Tis or high-grade dysplasia or carcinoma in situ, T1a and select superficial T1b tumors less than or equal to 2 cm without lymphovascular invasion). Since superficial tumors carry a low risk of lymph node involvement, local or distant recurrence, and death following endoscopic therapy, the less radical approach of ER is preferred in order to preserve the esophagus and spare patients from the morbidity of surgery [8]. Common endoscopic techniques include Endoscopic Mucosal Resection (EMR) or Endoscopic Submucosal Dissection (ESD) with or without ablative treatments including Radiofrequency Ablation (RFA), cryoablation, and Photodynamic Therapy (PDT). With close to 90% of all relapses occurring within the first two years after local therapy, the NCCN outlines guidelines by stage for careful surveillance with upper GI endoscopy (EGD) [9]. In tumors invading the submucosa, the risk of lymph node spread is as high as 20% [10]. Therefore, patients with such tumors should be evaluated for esophagectomy. Numerous studies have shown that risk of lymph node invasion may differ depending on the depth of pT1b tumors. Because of this, some experts favor pragmatically dividing the submucosa into equal thirds (sm1/2/3) in order to determine whether endoscopic therapy or esophagectomy is indicated [11]. Regardless of histology, esophagectomy can be performed in a number of ways depending on the location, disease extent, and preference and expertise of the surgeon.

Esophagectomy, either as initial therapy or after neoadjuvant therapy, can be performed with curative intent in early, resectable

thoracic (greater than 5 cm from cricopharyngeus) and intraabdominal esophageal and EGJ cancer. Resectable disease includes persistent disease with positive margins after ER, localized tumors, M0 disease if primary tumors do not go beyond the pleura, pericardium, and diaphragm (T1b-T4a) with or without regional lymph node involvement, select instances of recurrence, long segment intramucosal lesions not amenable to endoscopic therapy, and in rare occasions when the patient prefers a more radical approach. While the extent of lymphadenectomy is in question, the number of lymph nodes removed is an independent predictor of survival after esophagectomy, with significant reductions in mortality after removal of 12 or more lymph nodes [12-14]. The NCCN recommends removing a minimum of 15 lymph nodes in patients without prior chemoradiation therapy (CRT). The optimal number of lymph node removal in patients with prior CRT is unknown.

Though therapeutic esophagectomy yields high cure-rates, precise pathological staging, and low risk of recurrence in select patients with early stage cancer, performing an esophagectomy is not without risks. It is a technically challenging procedure, with success rates mirroring the volume of experienced surgeons and volume of esophagectomy surgeries performed at an institution [15,16]. Anastomotic leaks, severe pneumonia, atelectasis, intrathoracic hemorrhage, and recurrent laryngeal nerve injury are complications that can lead to long-term debilitation or potentially death [17-19]. Thus, careful and proper patient selection is critical. In addition to medically unfit patients or patients refusing surgery, circumstances that preclude surgical intervention include early superficial disease that can be treated in a less radical approach with ER and locally advanced disease with invasion of the aorta or in dangerous proximity to the heart or other vital structures. The only exception being in select cases where neoadjuvant therapy significantly downsizes the tumor, allowing for resection. Similarly, cervical or cervicothoracic esophageal cancer less than 5 cm from the cricopharyngeus is no longer treated surgically due to the high morbidity of esophagectomy, which often requires laryngectomy. Lastly, resection of a primary tumor in the presence of distant metastasis does not improve survival; thus advanced, metastatic disease is not treated surgically (Table 1).

Transhiatal	Upper midline laparotomy and left neck incisions allow dissection of the middle and distal thirds of the esophagus. Thoracic esophagus is mobilized and blunt dissection through the diaphragmatic hiatus is performed. A gastric tube is created, and anastomosis is made with cervical esophagus. Some studies have shown that transhiatal esophagectomy is associated with a lower 30-day morbidity and mortality compared to the transthoracic approach; however, some studies report better oncologic outcomes with en bloc transthoracic esophagectomy [20-23].
Ivor-Lewis Transthoracic	This technique involves right thoracotomy and abdominal laparotomy. Esophagus is divided at or above the level of the azygous vein. Gastric tube, like the one employed in transhiatal esophagectomy, is created and anastomosed at this location.
Tri-incisional (McKeown)	Three incisions are made, combining thoracotomy, laparotomy, and neck incision. Thoracotomy allows en bloc resection including esophagus and mediastinal and upper abdominal lymph nodes. Laparotomy is utilized for abdominal exploration and stomach mobilization for gastric conduit. Lastly, neck incision allows exposure to create an esophagogastric anastomosis.
Minimally invasive	A minimally invasive technique, as compared to the aforementioned open esophagectomy approaches, provides smaller incisions, less blood loss, decreased postoperative pain, faster return to bowel function, decreased ICU and hospital stay, and improved cosmetic appearance compared to the conventional open procedures [24]. With this technique, surgeons are able to perform with or without thoracoscopic dissection of intrathoracic esophagus.

Table 1: Esophagectomy Techniques.

Multimodality Therapy

Multimodality therapy combining the cytotoxicity of chemotherapy and sensitizing effects of RT with surgery is given with curative intent and is not given in the context of metastatic disease. In locally advanced disease, a number of studies have shown that treatment with trimodality therapy with concurrent chemotherapy and RT followed by surgery is superior to monotherapy with either surgery or RT. Treatment with surgery alone is associated with higher recurrence rates and poorer Overall Survival (OS) compared to multimodality therapy [25]. The 5-year survival rates associated with RT at conventional doses is only 0-10%. Thus, monotherapy with RT is not curative and is reserved for palliation or for those who are unable to tolerate chemotherapy [26-28]. Such poor long-term outcomes with monotherapy further strengthen the need for a multimodality approach.

Preoperative Chemoradiation Therapy

Preoperative or neoadjuvant therapy is treatment given prior to surgery with the potential to downsize tumors, to minimize micrometastatic disease, and to decrease risk of subsequent distant metastasis. Neoadjuvant therapy commonly consists of combined modality treatment with chemotherapy and RT. It is the most commonly used treatment approach in resectable disease, with curative intent. At least two randomized trials and many meta-analysis studies have demonstrated that trimodality therapy with neoadjuvant CRT is associated with superior outcomes compared to surgery alone in resectable disease [29,30].

The phase III CROSS trial consisted of 368 patients (75% adenocarcinoma, 23% ESCC) with potentially resectable esophageal or EGJ tumors. Patients were randomly assigned to either surgery upfront or preoperative CRT with weekly paclitaxel and carboplatin concurrently given with 41.4 Gy of RT [25]. The preoperative CRT arm was associated with acceptable toxicity, higher complete (R0) resection rates (92% vs. 65%), and longer median survival (49 vs. 24 months). At a median follow-up of 24 months, those in the preoperative CRT arm had a more significant reduction in overall rate of recurrence (35% vs. 58%) compared to the arm with surgery alone. Preoperative CRT also showed reduced locoregional recurrence from 34% to 14% ($P < 0.001$) and peritoneal carcinomatosis from 14% to 4% ($P < 0.001$) [31]. Based on these findings, preoperative CRT followed by surgery was established as one of the standard treatments for potentially curable esophageal and EGJ cancer.

The CALGB 9781 was a smaller randomized trial comparing trimodality therapy with RT and combination fluorouracil and cisplatin versus surgery alone in patients with stage I-III esophageal and EGJ cancer [32]. The study was prematurely closed due to poor accrual with only 42 and 14 patients with EAC and ESCC, respectively. Of the 25 accessible patients receiving trimodality therapy, 10 achieved pathologic complete response (pCR) (40%). Though not statistically significant, those in the trimodality arm also had longer 5-year survival rates than the arm with surgery alone (39% vs. 16%). Results showed no significant difference in perioperative morbidity or mortality.

The phase III randomized trial Federation Francophone de Cancerologie Digesetive (FFCD 9901) investigated the use of preoperative CRT using cisplatin and continuous infusion fluorouracil with 45 Gy of RT versus surgery alone in resectable stage I and II thoracic ESSC or EAC [33]. The trial was terminated after enrolling 195 patients due to an interim analysis showing low probability of demonstrating superiority of either arms. Compared to surgery alone, preoperative CRT did not improve R0 resection rates or 3-year survival rates, but rather showed higher postoperative mortality. Preoperative CRT with FOLFOX (fluorouracil, oxaliplatin, folinic acid) in locally advanced esophageal and EGJ cancers of both squamous cell carcinoma and adenocarcinoma are ongoing [34].

Postoperative Chemoradiation Therapy

Postoperative CRT is one of the standards of care for patients with completely resected gastric or EGJ adenocarcinoma who have not previously received preoperative therapy. The Intergroup 0116 (SWOG 9008/INT-0116) randomized phase III trial evaluated the benefit of surgery followed by CRT in patients with >T3 and/or node-positive gastric cancers [35]. Patients were assigned to either surgery alone or surgery followed by CRT consisting of bolus fluorouracil and leucovorin. After a median follow-up of over 10 years, OS and Relapse-Free Survival (RFS) showed continued benefit from postoperative CRT.

Definitive Chemoradiation Therapy

For patients who are medically unfit for surgery or have inoperative disease, definitive CRT is an appropriate choice. The RTOG 85-01 study compared the use of definitive CRT versus RT alone in patients with ESCC or EAC who were medically unfit for surgery. Patients who received the combined CRT therapy had a significantly better median survival (12.5 vs. 8.9 months), 5-year survival (26% vs. 0%), and lower incidence of local ($P < 0.02$) and distant recurrences ($P < 0.01$) compared to those randomized to the RT alone arm [36,37]. Based on these results, definitive CRT is one of the treatment options for unresectable locally advanced esophageal cancer. A follow up trial, INT-0123 showed that higher doses of RT (64.8 Gy) were not associated with improved local-regional control or survival compared to the standard RT dose (50.4 Gy) [38].

The FFCD 9102 study was a randomized trial that compared CRT alone with CRT followed by surgery in patients who were considered responders to CRT with locally advanced ESCC [39]. Patients with operable T3N0-1M0 thoracic esophageal cancer received fluorouracil and cisplatin and either conventional or split course concomitant RT. Patients were randomized to either surgery or continuation of CRT. The results suggested that patients responding to CRT have no additional benefit from surgery. The median survival was 17.7 months for those who had surgery compared to 19.3 months in the no surgery arm. The 3-month mortality rate was 9.3% for the surgery arm compared to 0.8% in the no surgery arm. Analysis of the Cochrane database also supported these findings showing that addition of esophagectomy in patients with localized ESCC with good responses to CRT provides little to no difference in OS and may be associated with higher treatment mortality [40].

The NCCN guidelines recommend paclitaxel and carboplatin, fluorouracil and oxaliplatin, fluorouracil and cisplatin (with capecitabine as a suitable replacement for fluorouracil) as preferred regimens for definitive CRT. Some studies also support

the use of docetaxel and cisplatin, carboplatin and paclitaxel, and FOLFOX [41-43].

Preoperative Chemotherapy

The role of preoperative chemotherapy in patients with locally advanced esophageal cancer was investigated in a number of randomized clinical trials. In the Intergroup trial, 467 patients with potentially resectable ESCC or EAC were randomized to receive preoperative chemotherapy with cisplatin and fluorouracil followed by surgery or surgery alone [44]. At a median follow-up of 8.8 months, preoperative chemotherapy decreased the incidence of microscopic residual cancer (R1) resection (4% vs. 15%); However, there was no difference in OS between the groups.

The Medical Research Council Oesophageal Cancer Working Group (MRC-OE02) was a much larger randomized trial that favored a different conclusion [45]. The trial included 802 patients with potentially resectable esophageal cancer of any histology. Patients were randomly assigned to preoperative cisplatin and fluorouracil followed by surgery or surgery alone. The decision to give patients preoperative RT was based on the clinicians' choosing. At a median follow-up of 6 years, those who received preoperative chemotherapy had superior disease-free survival and OS than those who underwent surgery alone. Postoperative complications were reported in 41% of patients in the preoperative chemotherapy arm and 42% in surgery alone arm. The authors concluded that preoperative cisplatin and fluorouracil improved survival without additional serious adverse events in the treatment of patients with resectable esophageal cancer. The French study, FNLCC ACCORD07-FFCD 9703, also compared preoperative cisplatin and fluorouracil followed by surgery with surgery alone. Preoperative cisplatin and fluorouracil was found to improve disease-free survival and OS in patients with resectable adenocarcinoma of the stomach and lower esophagus [46]. The Medical Research Council OE05 trial compared neoadjuvant ECX (epirubicin, oxaliplatin, capecitabine) with cisplatin and fluorouracil in patients with adenocarcinoma of the thoracic esophagus and EGJ [47]. ECX did not improve OS and was associated with higher toxicity. For this reason, preoperative chemotherapy with fluorouracil and cisplatin is recommended for adenocarcinoma of the thoracic esophagus and EGJ.

Two meta-analysis studies also showed survival benefit with use of preoperative chemotherapy in patients with resectable esophageal cancer compared to surgery alone. Sjoquist, et al. updated a previous meta-analysis with originally seventeen studies and an additional seven comparing neoadjuvant CRT or chemotherapy to surgery alone. They determined that neoadjuvant CRT or chemotherapy provided survival benefit compared to surgery alone in patients with resectable disease. However, it is not clear whether there is an advantage of neoadjuvant CRT over preoperative chemotherapy [29]. A second report by Kidane, et al. analyzed a total of 13 randomized trials and found that preoperative chemotherapy plus surgery was associated with superior survival advantage compared to surgery alone in patients with resectable thoracic esophageal cancer, with added toxicity from chemotherapy ranging from 11-90% [48].

Perioperative Chemotherapy

The MAGIC trial was a phase III randomized study performed by the British Medical Research Council [49]. The results of this trial established the role of perioperative chemotherapy with ECF (epirubicin, cisplatin, and fluorouracil) as a standard treatment for resectable gastric and EGJ adenocarcinoma. Over 500 patients were randomly assigned to perioperative ECF and surgery or surgery alone. ECF resulted in decreased tumor size and stage. With a median follow up of 4 years, the perioperative-chemotherapy group had higher likelihood of OS (Hazard Ration [HR] for death, 0.75; 95% Confidence Interval [CI], 0.60-0.93; P = 0.009; 5-year survival rate, 36% vs. 23%) and Progression-Free Survival (PFS) (HR for progression, 0.66; 95% CI, 0.53-0.81; P < 0.001). Perioperative fluorouracil and cisplatin is another viable treatment option for those with locally advanced resectable gastroesophageal cancers. In the FNCLCC and FFCD multicenter phase III trial, Ychou, et al. reported that treatment with perioperative fluorouracil and cisplatin for resectable adenocarcinoma of the lower esophagus, EGJ, and stomach was associated increased curative resection rate, disease-free survival, and OS compared to surgery alone [50].

With previously reported efficacy in docetaxel, researchers at the Institute of Clinical Oncology Research in Germany conducted the FLOT4 phase III clinical trial which compared perioperative chemotherapy with docetaxel, oxaliplatin, fluorouracil, and leucovorin (FLOT) to epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) in the treatment of locally advanced, resectable gastric or EGJ adenocarcinoma [51,52]. Compared to ECF/ECX, FLOT was associated with longer PFS (30 months vs. 18 months, HR 0.75, P = 0.004), more R0 resection rates (84% vs. 77%, P = 0.011), higher number of pT0 and pT1 tumors (25% vs. 15%, P = 0.001), as well as longer OS (50 months vs. 35 months, HR 0.77, CI, 0.63-0.94, P = 0.012). FLOT results in a 10% increase change in pCR, even in patients with advanced age, small tumors, negative nodal status, or signet cell components - factors that were once considered reasons to avoid perioperative therapy. In addition, FLOT administration is more convenient and consists of a single 24-hour infusion every 2 weeks instead of the continuous infusion used with ECF. With no significant differences in perioperative complications between the groups, results suggest perioperative FLOT is a superior regimen.

Systemic Therapy

As discussed in the previous sections, a number of chemotherapy regimens given concurrently with RT are used as

part of multimodality therapy for localized and locally advanced disease. For patients with locally advanced unresectable and metastatic disease who desire systemic therapy and have adequate performance status, combination chemotherapy is the best approach, since it may better limit disease and provide symptomatic relief from dysphagia, nausea, obstruction, perforation, bleeding, and pain. Treatment is guided by the histological subtype of esophageal cancer and HER2 tumor status.

Chemotherapy for Locally Advanced Unresectable and Metastatic Disease

First-line therapy for metastatic disease is a two-drug chemotherapy regimen. A third chemotherapy drug can be given to patients who are able to tolerate the toxicities of added therapy. Though the optimal regimen is not clear, cisplatin-based therapies are thought to be superior to non-cisplatin-containing regimens [53]. Tumor assessment for HER2 expression, PD-L1 overexpression, and dMMR are important for guiding therapy. Factors to consider include patient performance status, comorbidity, quality of life, patient preference, histologic type, and availability of clinical trials.

Targeted Therapy

Human Epidermal Growth Factor Receptor 2 (HER2), involved in cell proliferation and differentiation, is overexpressed in 15-30% of EAC and 5-13% in ESCC [54-57]. HER2 overexpression can be targeted by trastuzumab, a monoclonal antibody against HER2. In the Trastuzumab for Gastric or Gastro-oesophageal Junction center (ToGA) open-label international phase III trial, 594 patients with HER2-positive, locally advanced, recurrent, or metastatic gastric or EGJ adenocarcinoma were randomized to receive trastuzumab plus chemotherapy (cisplatin plus fluorouracil or capecitabine) or chemotherapy alone [58]. Those receiving trastuzumab plus chemotherapy demonstrated a higher median OS of 13.8 months compared to 11.1 months in those only treated with chemotherapy. The prognostic use of HER2 expression in esophageal adenocarcinoma remains unclear. Regardless, trastuzumab is recommended as first-line chemotherapy in combination with fluoropyrimidine and cisplatin for patients with HER2 overexpression in metastatic adenocarcinoma. In a small retrospective study, trastuzumab in combination with a modified FOLFOX regimen showed an acceptable safety profile for patients with HER2-positive gastroesophageal cancers; however further investigation with prospective studies are needed [59].

Elevated levels of Vascular Endothelial Growth Factor (VEGF), a key contributor in tumor angiogenesis and hematogenous spread, are associated with a poor prognosis in gastric and EGJ adenocarcinomas [60]. Ramucirumab, a VEGFR-2 antagonist monoclonal antibody, has shown therapeutic value in two trials leading to its approval in previously treated gastric and EGJ adenocarcinoma. In the REGARD trial, patients with progression after first-line platinum-containing or fluoropyrimidine-containing chemotherapy were randomly assigned to receive best supportive care plus either ramucirumab or placebo [61]. The arm receiving ramucirumab had superior median PFS (2.1 vs. 1.3 months) and OS (5.2 vs. 3.8 months) compared to those who received placebo. Similarly, in the RAINBOW trial, the efficacy of paclitaxel plus ramucirumab versus paclitaxel plus placebo was assessed in patients with metastatic gastric or EGJ adenocarcinoma who experienced disease progression after the first-line chemotherapy [62]. The median OS (9.6 vs. 7.4 months) and PFS (4.4 vs. 2.9 months) were significantly better in the ramucirumab arm compared to the placebo arm. Other VEGF-blocking agents such as bevacizumab and apatinib, tyrosine kinase inhibitors like sunitinib and sorafenib, and mTOR inhibitors are being investigated, but have not yet been approved by the FDA.

Epidermal Growth Factor Receptor (EGFR) may also play a role within the tumor microenvironment of esophageal cancer. Overexpression of EGFR results in dysregulated cell proliferation and apoptosis. In colorectal cancer, elevated levels of EGFR are associated with tumor growth, metastasis, and resistance to chemotherapy [63]. In the treatment of colorectal cancer, absence of an activating KRAS mutation is highly predictive of response to anti-EGFR therapy [64]. Anti-EGFR therapies have been studied in patients with gastric or EGJ adenocarcinoma, but trials with cetuximab and panitumumab have not shown benefit compared to standard first-line therapies. The utility of KRAS as a biomarker for response to anti-EGFR therapy for esophageal cancer is not known [65-67].

Immunotherapy

Cancer immunotherapy revolves around the relationship between the tumor microenvironment and the ability of the immune system to prevent and eliminate cancer cells. Tumors escape immune surveillance through upregulation of programmed cell death ligand 1 (PD-L1, also called B7-H1 or CD274), interfering with T-cell activation and antitumor responses. PD-L1 is overexpressed in 40% of esophagogastric cancers and is associated with cancer progression and poor postoperative prognosis [68,69]. Pembrolizumab and nivolumab are monoclonal antibodies that inhibit PD-1 pathways and promote antitumor responses in esophageal cancer and other noncolorectal gastrointestinal cancers, demonstrated by the KEYNOTE and CheckMate-032 trials. Unfortunately, the antitumor activity of these drugs seems less in esophageal cancer compared to that in melanoma and lung cancers.

The phase Ib KEYNOTE-012 trial was the first trial showing that use of pembrolizumab in patients with recurrent or metastatic PD-L1 positive EGJ or gastric adenocarcinoma

with two or more prior therapies was associated with antitumor activity and manageable toxicity [70]. In the phase II cohort 1 of the KEYNOTE-059 trial, the role of pembrolizumab monotherapy was evaluated in 259 patients with EGJ or gastric adenocarcinoma who progressed on two or more therapies [71]. In patients with PD-L1 positive tumors (n=143, 57.1%), the objective response rate (ORR) was 15.5%, with 2% of patients achieving complete response (CR). The median duration of response was 16.3 months. Cohorts 2 and 3 of KEYNOTE-059 are ongoing and will evaluate efficacy of first line monotherapy pembrolizumab or in combination with chemotherapy. The phase Ib KEYNOTE-028 trial extended participation to patients with either EAC or ESCC previously treated with two or more therapies [72]. Together, ESCC and EAC had an ORR of 30% and a median duration of response of 15 months. Separated by histologic subtype, patients with EAC were found to have superior ORR to ESCC (40% vs. 28%).

Disagreement exists as to the optimal timing for a trial of pembrolizumab. In the U.S., pembrolizumab is approved as third-line therapy in patients with PD-L1-expressing tumors (Combined positive score [CPS] 1 or higher) after failure of two separate chemotherapy regimens. However, evidence from two phase III trials support pembrolizumab as an appropriate second-line therapy. The KEYNOTE-181 trial showed superiority of pembrolizumab over chemotherapy for second-line treatment in patients with ESCC and adenocarcinoma of the esophagus or EGJ, Siewert type I, with a higher level of PD-L1 expression (CPS 10 or higher) [73]. In a preliminary report presented at the 2019 ASCO Gastrointestinal Cancers Symposium, of the 222 patients with PD-L1 positive tumors (CPS 10 or higher), the group treated with pembrolizumab had superior median OS, twice as many individuals alive, and fewer grade 3 to 5 drug-related adverse events compared to the chemotherapy group. In the KEYNOTE-061 trial, 592 patients with advanced gastric or EGJ cancer that had progressed on combination chemotherapy with platinum and fluoropyrimidine were assigned to receive either pembrolizumab or paclitaxel monotherapy. While pembrolizumab did not significantly prolong OS and only achieved similar ORR to the paclitaxel group, pembrolizumab was associated with a better adverse event profile. In post hoc analysis, the treatment effect of pembrolizumab was greatest in patients with PD-L1 CPS of 10 or greater and for those whose tumors were MSI-H, regardless of CPS status [74].

Predictive factors for therapeutic response to PD-1 blockade include PD-L1 overexpression, microsatellite instability, and high tumor antigen load. Microsatellite instability (MSI, microsatellite instability-high or MSI-H) is a condition of hyper-mutability stemming from mismatch repair-deficient tumors (dMMR). These tumors make up to fifteen percent of colorectal cancers and have 10-100 times more somatic mutations in repair genes compared to mismatch repair-proficient tumors (pMMR), or tumors without defects in mismatch repair [75-77]. Roughly 3% are associated with Lynch syndrome (mutations in MSH2, MLH1, MSH6, and PMS2) and the remaining 12% are products of sporadic mutations with hypermethylation of the MLH1 gene promoter [78,79]. Tumors with MSI are thought to be more responsive to checkpoint inhibitors due to generation of neoantigens which may be recognized as "non-self" immunogenic antigens. The MK-3475 phase II study evaluated the therapeutic response of pembrolizumab in patients with progressive metastatic carcinoma with and without MSI. They found that dMMR tumors were more easily recognized by the immune system and were more susceptible to pembrolizumab. Compared to pMMR tumors, dMMR tumors had higher numbers of somatic mutations that correlated with prolonged PFS. Based on this trial, clinicians are better equipped in predicting response to pembrolizumab with MSI status in not only colorectal cancer, but also for unresectable or metastatic solid tumors of any origin [80].

In May 2017, the FDA approved pembrolizumab for the treatment of unresectable of metastatic MSI-H or dMMR solid tumors that have progressed with prior treatment and have no satisfactory alternative therapy options. Shortly after, in September 2017, FDA approval was extended to patients with PD-L1-overexpressing gastric and EGJ adenocarcinomas previously treated with two or more prior therapies with or without HER-2neu targeted therapy [81].

The safety and efficacy of nivolumab has also been demonstrated in patients with advanced, treatment refractory gastroesophageal adenocarcinoma and squamous cell carcinoma. The phase 3 ONO-4538 ATTRACTION 2 trial was the first immunotherapy trial to show improved survival benefit for patients with heavily pretreated gastric or gastroesophageal cancer [82]. The phase I/II, open-label CheckMate-032 study included 160 patients with advanced or metastatic esophageal, gastric, or EGJ cancer who progressed on one or more chemotherapy regimens. Patients were randomly assigned to nivolumab alone or a combination of ipilimumab, an anti CTLA-4 monoclonal antibody, and nivolumab [83]. Nivolumab with or without ipilimumab led to durable responses and long-term OS, regardless of PD-L1 status. Like the KEYNOTE-059 trial, it was also noted that PD-L1 positive patients had superior response rates (27%) compared to PD-L1 negative patients (12%). Only 17% of patients experienced grade 3 or 4 adverse effects, similar to studies done in other tumor types. Together, the CheckMate-032 and KEYNOTE trials suggest PD-1 blockade as a safe and effective treatment in both ESCC and EAC in pretreated patients.

Avelumab, another monoclonal antibody against PD-L1, has not been shown to improve OS or PFS in patients with esophagogastric cancer [84]. Likewise, ipilimumab has not been proven to lengthen immune-related progression-free survival and has a median survival comparative to best supportive care [85].

Studies investigating other immunotherapies for esophagogastric cancers are underway.

Summary

Major leaps have been made in advancing the science of treating esophageal cancer. Diagnostic and therapeutic endoscopy is essential in the management from early disease to palliation of advanced disease. Innovative techniques enable radiation oncologists to deliver more precise RT with improved efficacy and less toxicity. Improvements in surgical approach have reduced treatment morbidity and mortality. The application of the knowledge learned from molecular profiling in esophageal cancer has led to clinical investigations of novel agents targeting those changes. We are now living in the era of individualized medicine to identify the patients who will benefit the most, and have the least toxicity, from specific therapies. Following the breast cancer lead, HER2/neu is a clear target in the treatment of esophageal cancer. Patients with MSI-positive tumors represent individuals predicted to have favorable responses to checkpoint inhibition. Immunotherapy is generally less toxic and is associated with more durable responses in molecularly selected upper GI cancers. Trials looking at predictors of response are underway. The overall outcome from this disease, however, remains far from satisfactory. Clinical trials investigating strategies in prevention, early diagnosis, and treatment of early and advanced disease are guided by lessons learned in epidemiology, molecular genetics, pharmacogenomics, and precision medicine.

References

1. SEER Cancer Stat Facts: Esophageal Cancer. National Cancer Institute. Bethesda.
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, et al. (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136: E359-386.
3. Dulak AM, Stojanov P, Peng S, Lawrence MS, Fox C, et al. (2013) Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity. Nat Genet 45: 478-486.
4. Arnold M, Laversanne M, Brown LM, Devesa SS, Bray F (2017) Predicting the Future Burden of Esophageal Cancer by Histological Subtype: International Trends in Incidence up to 2030. Am J Gastroenterol 112: 1247-1255.
5. Cancer Genome Atlas Research N, Analysis Working Group: Asan U, Agency BCC, Greater Poland Cancer Centre, Harvard Medical School, et al. (2017) Integrated genomic characterization of oesophageal carcinoma. Nature 541: 169-175.
6. Rice TW, Gress DM, Patil DT, Hofstetter WL, Kelsen DP, et al. (2017) Cancer of the esophagus and esophagogastric Junction-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 67: 304-317.
7. Rice TW, Apperson-Hansen C, DiPaola LM, Semple ME, Lerut TE, et al. (2016) Worldwide Esophageal Cancer Collaboration: clinical staging data. Dis Esophagus 29: 707-714.
8. Berry MF, Zeyer-Brunner J, Castleberry AW, Martin JT, Gloor B, et al. (2013) Treatment modalities for T1N0 esophageal cancers: a comparative analysis of local therapy versus surgical resection. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer 8: 796-802.
9. National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction 2019.
10. Rustgi AK, El-Serag HB (2014) Esophageal carcinoma. N Engl J Med 371: 2499-2509.
11. Manner H, Pech O (2015) Measurement of the tumor invasion depth into the submucosa in early adenocarcinoma of the esophagus (pT1b): Can microns be the new standard for the endoscopist? United European gastroenterology journal 3: 501-504.
12. Peyre CG, Hagen JA, DeMeester SR, Van Lanschot JJ, Hölscher A, et al. (2008) Predicting systemic disease in patients with esophageal cancer after esophagectomy: a multinational study on the significance of the number of involved lymph nodes. Ann Surg 248: 979-985.
13. Rizk NP, Ishwaran H, Rice TW, Chen LQ, Schipper PH, et al. (2010) Optimum lymphadenectomy for esophageal cancer. Ann Surg 251: 46-50.
14. Groth SS, Virnig BA, Whitson BA, DeFor TE, Li ZZ, et al. (2010) Determination of the minimum number of lymph nodes to examine to maximize survival in patients with esophageal carcinoma: data from the Surveillance Epidemiology and End Results database. J Thorac Cardiovasc Surg 139: 612-620.
15. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL et al. (2002) Hospital volume and surgical mortality in the United States. N Engl J Med 346: 1128-1137.
16. Dimick JB, Wainess RM, Upchurch GR, Jr., Iannettoni MD, Orringer MB (2005) National trends in outcomes for esophageal resection. Ann Thorac Surg 79: 212-216.
17. Moraca RJ, Low DE (2006) Outcomes and health-related quality of life after esophagectomy for high-grade dysplasia and intramucosal cancer. Arch Surg 141: 545-549.
18. Viklund P, Wengstrom Y, Rouvelas I, Lindblad M, Lagergren J (2006) Quality of life and persisting symptoms after oesophageal cancer surgery. Eur J Cancer 42: 1407-1414.
19. Reynolds JV, McLaughlin R, Moore J, Rowley S, Ravi N, et al. (2006) Prospective evaluation of quality of life in patients with localized oesophageal cancer treated by multimodality therapy or surgery alone. Br J Surg 93: 1084-1090.
20. Hulscher JB, Tijssen JG, Obertop H, van Lanschot JJ (2001) Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. Ann Thorac Surg 72: 306-313.
21. Hulscher JB, van Sandick JW, de Boer BPL, Tijssen JGP, et al. (2002) Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 347: 1662-1669.
22. Omloo JM, Lagarde SM, Hulscher JB, Reitsma JB, Fockens P, et a. (2007) Extended transthoracic resection compared with limited tran-

shiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg 246: 992-1000.

23. Omloo JM, Law SY, Launois B, Le Prisé E, Wong J, et al. (2009) Short and long-term advantages of transhiatal and transthoracic oesophageal cancer resection. Eur J Surg Oncol 35: 793-797.

24. Santillan AA, Farma JM, Meredith KL, Shah NR, Kelley ST (2008) Minimally invasive surgery for esophageal cancer. J Natl Compr Canc Netw 6: 879-884.

25. Shapiro J, van Lanschot JJB, Hulshof M, van Hagen P, van Berge Henegouwen MI, et al. (2015) Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 16: 1090-1098.

26. Newaishy GA, Read GA, Duncan W, Kerr GR (1982) Results of radical radiotherapy of squamous cell carcinoma of the oesophagus. Clin Radiol 33: 347-352.

27. Okawa T, Kita M, Tanaka M, Ikeda M (1989) Results of radiotherapy for inoperable locally advanced esophageal cancer. Int J Radiat Oncol Biol Phys 17: 49-54.

28. Sun DR (1989) Ten-year follow-up of esophageal cancer treated by radical radiation therapy: analysis of 869 patients. Int J Radiat Oncol Biol Phys 16: 329-334.

29. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, et al. (2011) Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 12: 681-692.

30. Pasquali S, Yim G, Vohra RS, Mocellin S, Nyanhongo D, et al. (2017) Survival After Neoadjuvant and Adjuvant Treatments Compared to Surgery Alone for Resectable Esophageal Carcinoma: A Network Meta-analysis. Ann Surg 265: 481-491.

31. Oppedijk V, Gaast Avd, Lanschot JJB, van Hagen P, van Os R, et al. (2014) Patterns of Recurrence After Surgery Alone Versus Preoperative Chemoradiotherapy and Surgery in the CROSS Trials. Journal of Clinical Oncology 32: 385-391.

32. Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, et al. (2008) Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 26: 1086-1092.

33. Mariette C, Dahan L, Mornex F, Maillard E, Thomas PA, et al. (2014) Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol 32: 2416-2422.

34. Messager M, Mirabel X, Tresch E, Paumier A, Vendrely V, et al. (2016) Preoperative chemoradiation with paclitaxel-carboplatin or with fluorouracil-oxaliplatin-folinic acid (FOLFOX) for resectable esophageal and junctional cancer: the PROTECT-1402, randomized phase 2 trial. BMC Cancer 16: 318.

35. Smalley SR, Benedetti JK, Haller DG, Hundahl SA, Estes NC, et al. (2012) Updated Analysis of SWOG-Directed Intergroup Study 0116: A Phase III Trial of Adjuvant Radiochemotherapy Versus Observation After Curative Gastric Cancer Resection. Journal of Clinical Oncology 30: 2327-2333.

36. Herskovic A, Martz K, al-Sarraf M, Leichman L, Brindle J, et al. (1992) Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 326: 1593-1598.

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

38. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, et al. (2002) INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 20: 1167-1174.

39. Bedenne L, Michel P, Bouche O, Milan C, Mariette C, et al. (2007) Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 25: 1160-1168.

40. Vellayappan BA, Soon YY, Ku GY, Leong CN, Lu JJ, et al. Chemoradiotherapy versus chemoradiotherapy plus surgery for esophageal cancer. Cochrane Database Syst Rev 8: CD010511.

41. Li QQ, Liu MZ, Hu YH, Liu H, He ZY, et al. (2010) Definitive concomitant chemoradiotherapy with docetaxel and cisplatin in squamous esophageal carcinoma. Dis Esophagus 23: 253-259.

42. Ruppert BN, Watkins JM, Shirai K, Wahlquist AE, Garrett-Mayer E, et al. (2010) Cisplatin/Irinotecan versus carboplatin/paclitaxel as definitive chemoradiotherapy for locoregionally advanced esophageal cancer. Am J Clin Oncol 33: 346-352.

43. Conroy T, Galais MP, Raoul JL, Bouché O, Gourgou-Bourgade S, et al. (2014) Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. Lancet Oncol 15: 305-314.

44. Kelsen DP, Ginsberg R, Pajak TF, Sheahan DG, Gunderson L, et al. (1998) Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 339: 1979-1984.

45. Medical Research Council Oesophageal Cancer Working G (2002) Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 359: 1727-1733.

46. Boige V, Pignon J, Saint-Aubert B, Lasser P, Conroy T, et al. (2007) Final results of a randomized trial comparing preoperative 5-fluorouracil (F)/cisplatin (P) to surgery alone in adenocarcinoma of stomach and lower esophagus (ASLE): FNLCC ACCORD07-FFCD 9703 trial. Journal of Clinical Oncology 25: 4510-4510.

47. Alderson D, Langley RE, Nankivell MG, Blazeby JM, Griffin M, et al. (2015) Neoadjuvant chemotherapy for resectable oesophageal and junctional adenocarcinoma: Results from the UK Medical Research Council randomised OEO5 trial (ISRCTN 01852072). Journal of Clinical Oncology 33: 4002-4002.

48. Kidane B, Coughlin S, Vogt K, Malthaner R (2015) Preoperative chemotherapy for resectable thoracic esophageal cancer. Cochrane Database Syst Rev 2015: CD001556.

49. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, et al. (2006) Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 355: 11-20.

50. Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, et al. (2011) Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 29: 1715-1721.

51. Al-Batran S-E, Homann N, Schmalenberg H, Kopp HG, Haag GM, et al. (2017) Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A multicenter, randomized phase 3 trial. Journal of Clinical Oncology 35: 4004-4004.

52. Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, et al. (2019) Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2019.

53. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, et al. (2006) Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 24: 4991-4997.

54. Flejou JF, Paraf F, Muzeau F, Fékété F, Hénin D, et al. (1994) Expression of c-erbB-2 oncogene product in Barrett's adenocarcinoma: pathological and prognostic correlations. J Clin Pathol 47: 23-26.

55. Reichelt U, Duesedau P, Tsourlakis M, Quaas A, Link BC, et al. (2007) Frequent homogeneous HER-2 amplification in primary and metastatic adenocarcinoma of the esophagus. Mod Pathol 20: 120-129.

56. Vakiani E (2015) HER2 testing in gastric and gastroesophageal adenocarcinomas. Adv Anat Pathol 22: 194-201.

57. Mimura K, Kono K, Hanawa M, Mitsui F, Sugai H, et al. (2005) Frequencies of HER-2/neu expression and gene amplification in patients with oesophageal squamous cell carcinoma. Br J Cancer 92: 1253-1260.

58. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, et al. (2010) Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 376: 687-697.

59. Soularue E, Cohen R, Tournigand C, Zaanan A, Louvet C, et al. (2015) Efficacy and safety of trastuzumab in combination with oxaliplatin and fluorouracil-based chemotherapy for patients with HER2-positive metastatic gastric and gastro-oesophageal junction adenocarcinoma patients: a retrospective study. Bull Cancer 102: 324-331.

60. Fondevila C, Metges JP, Fuster J, Grau JJ, Palacín A, et al. (2004) p53 and VEGF expression are independent predictors of tumour recurrence and survival following curative resection of gastric cancer. Br J Cancer 90: 206-215.

61. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, et al. (2014) Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 383: 31-39.

62. Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, et al. (2014) Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 15: 1224-1235.

63. Sasaki T, Hiroki K, Yamashita Y (2013) The Role of Epidermal Growth Factor Receptor in Cancer Metastasis and Microenvironment. BioMed Research International 2013: 8.

64. Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, et al. (2009) Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 27: 663-671.

65. Lordick F, Kang YK, Chung HC, Salman P, Oh SC, et al. (2013) Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol 14: 490-499.

66. Waddell T, Chau I, Cunningham D, Gonzalez D, Okines AF, et al. (2013) Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol 14: 481-489.

67. Tebbutt NC, Price TJ, Ferraro DA, Wong N, Veillard AS, et al. (2016) Panitumumab added to docetaxel, cisplatin and fluoropyrimidine in oesophagogastric cancer: ATTAX3 phase II trial. Br J Cancer 114: 505-509.

68. Chen L, Xiong Y, Li J, Zheng X, Zhou Q, et al. (2017) PD-L1 Expression Promotes Epithelial to Mesenchymal Transition in Human Esophageal Cancer. Cell Physiol Biochem 42: 2267-2280.

69. Kelly RJ (2017) Immunotherapy for Esophageal and Gastric Cancer. Am Soc Clin Oncol Educ Book 37: 292-300.

70. Muro K, Chung HC, Shankaran V, Geva R, Catenacci D, et al. (2016) Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. Lancet Oncol 17: 717-726.

71. Fuchs CS, Doi T, Jang RW, et al. (2018) Safety and Efficacy of Pembrolizumab Monotherapy in Patients with Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial. JAMA Oncol 4: e180013.

72. Doi T, Piha-Paul SA, Jalal SI, Saraf S, Lunceford J, et al. (2018) Safety and Antitumor Activity of the Anti-Programmed Death-1 Antibody Pembrolizumab in Patients with Advanced Esophageal Carcinoma. J Clin Oncol 36: 61-67.

73. Kojima T, Muro K, Francois E, Hsu CH, Moriwaki T, et al. (2019) Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: Phase III KEYNOTE-181 study. Journal of Clinical Oncology 37: 2-2.

74. Shitara K, Ozguroglu M, Bang YJ, Di Bartolomeo M, Mandalà M, et al. (2018) Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet 392: 123-133.

75. Timmermann B, Kerick M, Roehr C, Fischer A, Isau M, et al. (2010) Somatic mutation profiles of MSI and MSS colorectal cancer identified by whole exome next generation sequencing and bioinformatics analysis. PLoS One 5: e15661.

76. Eshleman JR, Lang EZ, Bowerfind GK, Parsons R, Vogelstein B, et al. (1995) Increased mutation rate at the hprt locus accompanies microsatellite instability in colon cancer. Oncogene 10: 33-37.

77. Dolcetti R, Viel A, Doglioni C, Russo A, Guidoboni M, et al. (1999) High prevalence of activated intraepithelial cytotoxic T lymphocytes and increased neoplastic cell apoptosis in colorectal carcinomas with microsatellite instability. Am J Pathol 154: 1805-1813.

78. Peltomaki P (2005) Lynch syndrome genes. Fam Cancer 4: 227-232.

79. Boland CR, Goel A (2010) Microsatellite instability in colorectal cancer. Gastroenterology 138: 2073-2087.

80. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, et al. (2015) PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. New England Journal of Medicine 372: 2509-2520.

81. Fuchs CS, Doi T, Jang RW-J, Muro K, Satoh T, et al. (2017) KEYNOTE-059 cohort 1: Efficacy and safety of pembrolizumab (pembro) monotherapy in patients with previously treated advanced gastric cancer. Journal of Clinical Oncology 35: 4003-4003.

82. Kang Y-K, Satoh T, Ryu M-H, Chao Y, Kato K, et al. (2017) Nivolumab (ONO-4538/BMS-936558) as salvage treatment after second or later-line chemotherapy for advanced gastric or gastro-esophageal junction cancer (AGC): A double-blinded, randomized, phase III trial. Journal of Clinical Oncology 35: 2-2.

83. Janjigian YY, Ott PA, Calvo E, Kim JW, Ascierto PA, et al. (2017) Nivolumab ± ipilimumab in pts with advanced (adv)/metastatic chemotherapy-refractory (CTx-R) gastric (G), esophageal (E), or gastroesophageal junction (GEJ) cancer: CheckMate 032 study. Journal of Clinical Oncology 35: 4014-4014.

84. Bang YJ, Ruiz EY, Van Cutsem E, Lee KW, Wyrwicz L, et al. (2018) Phase III, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment of patients with advanced gastric or gastro-oesophageal junction cancer: primary analysis of JAVELIN Gastric 300. Ann Oncol 29: 2052-2060.

85. Bang YJ, Cho JY, Kim YH, Kim JW, Di Bartolomeo M, et al. (2017) Efficacy of Sequential Ipilimumab Monotherapy versus Best Supportive Care for Unresectable Locally Advanced/Metastatic Gastric or Gastroesophageal Junction Cancer. Clin Cancer Res 23: 5671-5678.