Chapter 8
Emerging Roles of Phytochemicals in the Pathobiology and Management of Esophageal Cancer

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Abstract Esophageal cancer demonstrates varying epidemiology across the globe. Over the last 30 years, esophageal adenocarcinoma has overtaken esophageal squamous cell cancer as the most common histologic variety in the Western hemisphere. However, esophageal squamous cell cancer remains the predominant type in Asia. Despite an increase in our understanding of its pathophysiology, varying chemotherapeutic regimens have not made any significant impact on the survival of patients with this disease. These chemotherapeutic agents have potentially severe adverse effects which affect the patient adherence to the given treatment. As an alternative modality of the disease treatment, various phytochemicals have been studied as therapeutic and prophylactic entities for esophageal cancer. Most of these agents exert their effect using antioxidant and anti-inflammatory pathways. In this chapter, we discuss the roles of curcumin, flavonoids, and other agents in terms of the available data. As we move towards preventative care among the high-risk

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patients with conditions such as Barrett's esophagus, supplementation of these phytochemicals may lead to halting and decrease in the progression towards malignancy. More robust studies are needed prior to recommending their widespread application; however, in the era of cost-effective medicine, introducing such options in the care of patients will have a significant impact in the long run. We also briefly discuss the current state of chemotherapeutic and immune therapeutic options for patients with esophageal cancer.

Keywords Phytochemicals · Cancer · Esophagus · Targeted therapies · Pathobiology · Management · Clinical outcomes

Abbreviations

BSC	Best supportive care
CD	Cluster differentiation
COX	Cyclooxygenase
CSC	Cancer stem cells
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
EAC	Esophageal adenocarcinoma
EGCG	Epigallocatechin gallate
EGFR	Epidermal growth factor receptor
ESC	Esophageal squamous cell cancer
FDA	Food and Drug Administration (USA)
FGFR	Fibroblast growth factor receptor
5-FU	5-Fluorouracil
GEJ	Gastroesophageal junctional carcinoma
GERD	Gastroesophageal reflux disease
HER2	Human epidermal growth factor receptor 2
IL	Interleukin
NF-kB	Nuclear factor-kB
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death protein 1
PDGFR	Platelet-derived growth factor receptor
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PGE-2	Prostaglandin E-2
ROS	Reactive oxygen species
RTK	Receptor tyrosine kinase
TKI	Tyrosine kinase inhibitors
VEGFR	Vascular endothelial growth factor receptor

1 Epidemiology of Esophageal Cancer

Esophageal cancer is one of the most common malignancies in the world and is the ninth most common malignancy overall [1]. However, in the United States, it accounts for nearly 1% of all the cancer diagnoses and is currently the 11th leading cause of cancer-related deaths [2]. In the United States, it is diagnosed most commonly in patients between the age of 65 and 74 years.

The two major subtypes of esophageal cancer are esophageal adenocarcinoma (EAC) and esophageal squamous cell cancer (ESC). Although globally 95% of all esophageal cancers are ESC, there are significant worldwide geographic differences. EAC has overtaken ESC as the predominant type in the developed countries, while ESC is still the most common variety in the African and East Asian countries [3]. Although the incidence of esophageal cancer in the United States has increased from 1975 till 2006, since then it has shown a steady decline. Both major varieties of esophageal cancers more commonly occur in men compared to women. The current age-adjusted annual incidence is 4.3 cases per 100,000 people [2]. This is in stark contrast to the "esophageal cancer belt" of Northern Iran, Northern China, Kazakhstan, and Uzbekistan, where the incidence of esophageal cancer (predominantly ESC) has been reported to be as high as 800 cases per 100,000 population [4].

The predominant risk factors for ESC include cigarette smoking, alcohol consumption, dietary use of N-nitroso compounds, deficiency of zinc, selenium, caustic strictures, Plummer-Vinson syndrome, and tylosis [5]. Comparatively, the predominant risk factors for EAC are gastroesophageal reflux disease (GERD) and metabolic syndrome since they increase the risk of Barrett's esophagus [6]. About 40% of the diagnosed cases have distant metastatic disease, and these patients have a 5-year survival of 19.9%. However, the 5-year survival is much better (46.7%) in patients with localized esophageal cancer. Despite the decline seen in the incidence of esophageal cancer over the last decade, the mortality rate and 5-year survival have not changed significantly. This has led to significant research to explore newer treatment strategies, including the use of phytochemicals, for the management of esophageal cancer.

2 The Role of Phytochemicals in the Treatment of Esophageal Cancer

Although the localized esophageal cancer is being increasingly managed with endoscopic resection strategies, the mainstay of the treatment for advanced esophageal cancer comprises a combination of surgery, chemotherapy, and/or radiation [7]. Despite significant advances in the diagnosis and treatment, the 5-year survival rate for the disease remains relatively low. The modalities in use for the treatment of esophageal cancers are known to have numerous side effects and, at times, limited efficacy given the usual late stage at which the disease is detected owing to the slow

onset of symptoms, a factor that significantly contributes to the dismal survival rate [8, 9]. Therefore, the need to identify novel treatment modalities remains high, not only in complementing the currently available treatment options but also in playing possible role(s) towards the prevention and management of the disease.

One such area of promise is the use of phytochemicals. The word phytochemical is originally derived from phyto which in Greek means related to plants. Phytochemicals are nonessential plant-based compounds found abundantly in fruits, vegetables, grains, etc. [10]. Though used for various ailments over centuries, the role of phytochemicals is only now being elucidated scientifically. Over the past few decades, numerous studies have identified a wide array of pharmacological effects for phytochemicals, particularly as antioxidants and anti-inflammatory agents while also possessing significant anticancer properties [11–14].

Phytochemicals are primarily classified into five groups, namely carotenoids, phenolics, alkaloids, nitrogen-containing compounds, and organo-sulfides [10]. Among these, most studies have been done on phenolics and carotenoids. The anticancer roles/properties of various phytochemicals are well documented in peer-reviewed studies pertaining to cancers of the gastrointestinal tract [11]. Here, we therefore discuss the role(s) of some of the most well-studied phytochemicals in the potential treatment and management of esophageal cancer.

3 Curcumin

Turmeric is a major spice in Asian cuisines and has been used for centuries in herbal medicine. By virtue of its antioxidant properties, it acts as an anti-inflammatory agent; studies have documented its role(s) in lowering the incidence of cancer [12]. It is one of the three curcuminoids in the spice, belonging to the subcategory of phenolic acids under the group phenolics [10, 13]. Curcumin possesses a significant anti-oncogenic profile owing to its effects on multiple molecular pathways involved in carcinogenesis such as its regulation of an array of membrane receptors, transcription factors, cytokines, kinases, and other enzymes [14–16]. The anticancer effects of curcumin in gastrointestinal malignancies such as esophageal, gastric, and colon cancers are well documented [11, 17–19]. Interestingly, a comparison of the effect of curcumin and 5-fluorouracil (5-FU) on esophageal squamous cell carcinoma found curcumin to be more effective [20].

In esophageal cancers, multiple molecular pathways are involved in the pathogenesis and progression of the disease (Fig. 8.1). The efficacy of curcumin on esophageal malignancies has been evaluated through various angles. Oxidative stress produced by reactive oxygen species (ROS) plays a significant role(s) in the development of many cancers, including those of the esophagus [21]. One study identified curcumin to exert an antioxidant and an anti-inflammatory effect on esophageal cell lines as a result of induction of the activity of superoxide dismutase-1, a potent antioxidant enzyme, and inhibition of the activity of cyclooxygenase-2, a pro-inflammatory protein, respectively [22]. Another study

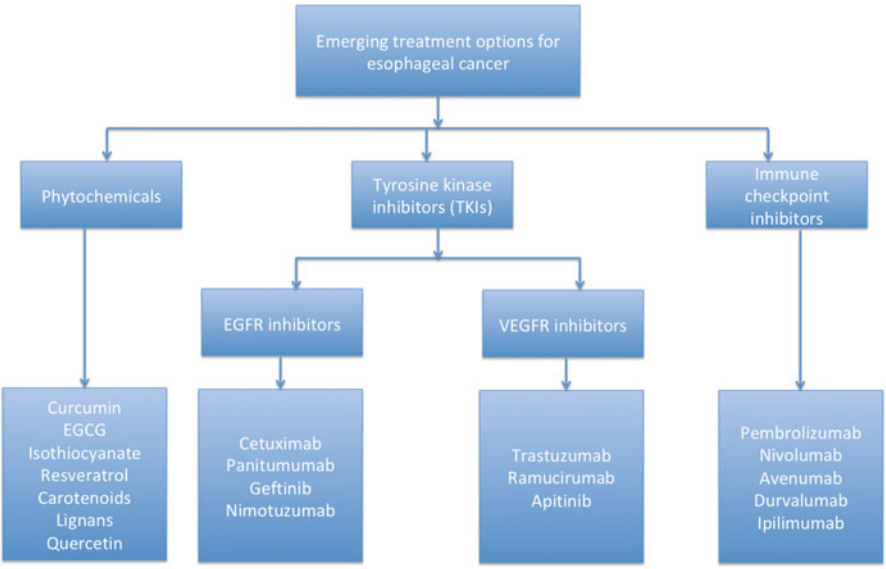

Fig. 8.1 Schematic representation of some of the emerging treatment options for the management of esophageal cancer

further expanded upon curcumin's anti-inflammatory role in esophageal tumorigenesis by highlighting its inhibition of nuclear factor (NF)-kB activity and interleukin (IL)-8 mRNA expression [23].

Curcumin promotes apoptosis and cell cycle arrest in esophageal cancer cells by inhibiting the Notch signaling pathway, a process known to be upregulated in many cases of esophageal cancers [24, 25]. In many tumors, such as esophageal squamous cell carcinoma, cancer stem cells (CSCs) are known to contribute to the poor prognosis of the disease [26, 27]. The CSCs differentiate into non-CSCs making up the bulk of these tumors [28]. Moreover, CSCs have also been found to add to the resistance of tumors towards the traditional chemo- and radiotherapies [29]. Curcumin has shown efficacy in targeting these CSCs in esophageal cancer [18].

4 Epigallocatechin Gallate

Besides phenolic acids from which curcumin traces its origin, another very-well-studied subcategory of phenolics is the flavonoids [10]. Flavonoids are found abundantly in fruits and tea [13]. Historically, green tea has been infamous in possessing numerous health benefits, ranging from its roles as an antibacterial and anti-inflammatory agent to its effects in cardioprotection and cancer prevention [30]. As far as green tea's anticancer role is concerned, researchers have identified

the catechin epigallocatechin gallate (EGCG) as the primary active agent [31]. Although abundant in green tea, the levels of EGCG in black tea are much lower as the catechin is oxidized during the production process of black tea leaves, explaining the difference in the anticancer effects of the two types of teas [32]. Studies have also found EGCG to exert its anticancer effects through a myriad of processes at the molecular level that control the development and progression of cancers, including but not restricted to proliferation of cancer cells, angiogenesis, metastasis, and oxidative stress [33–35] (Fig. 8.1).

Studies have identified the mechanism behind EGCG's anticancer role in esophageal cancer to be multifaceted and a combination of its anti-inflammatory effect, such as decreased COX-2 and PGE-2 production, and by inducing cell cycle arrest by inhibition of cyclin D1 [36]. Other mechanisms by which EGCG was found to inhibit progression of esophageal cancer cell lines was by blocking the phosphorylation of EGFR, thus leading to the inactivation of a potent growth receptor [37].

5 Isothiocyanate, Resveratrol, and Carotenoids

Besides curcumin and EGCG, other phytochemicals have also shown promise as anticancer agents against not just esophageal cancers but other cancers as well. Among these are the carotenoids, other flavonoids such as resveratrol and organosulfide isothiocyanate, etc. A meta-analysis conducted to study the association between the consumed amount of carotenoids and risk of developing esophageal cancers concluded that the risk of esophageal cancers is lowered with a higher intake of carotenoids [38]. Although the anticancer role of resveratrol for other gastrointestinal cancers is well established [11], recent studies have also identified its role against esophageal cancer, possibly by upregulating cancer cell apoptosis [39]. Similarly, isothiocyanate has also shown promise in combating esophageal cancer in mice; however, more investigations are needed to elucidate more about the precise molecular mechanisms involved in bringing about the effect [11, 40].

6 Lignans, Quercetin

The Western diet is rich in three phytochemicals that possess estrogenic properties, namely lignans, quercetin, and resveratrol [41–44]. A diet rich in wine, tea, vegetables, lettuce, whole-grain bread, and tomatoes and decreased intake of milk are a great source of all the three phytochemicals. These phytochemicals have a chemical structure similar to female hormones resulting in being able to bind to estrogenic receptors, and thus produce estrogenic effects [45–47]. Interestingly, in vitro studies have found estrogenic receptors in the esophageal tissue [48]. This is intriguing because the presence of estrogen has been postulated to be an important factor for the lower incidence of esophageal adenocarcinoma in females when compared to men

(women-to-men ratio of 9:1) [49]. Studies have also shown strong negative correlation between a diet rich in lignans, quercetin, and resveratrol and the incidence of various histological patterns of esophageal cancer [50]. Tea is a good source of lignans and quercetin, and animal studies have demonstrated anticancer properties of black tea [51]. In the European countries, whole-grain bread is found to be a good source of lignans, and the consumption of whole-grain bread has been associated with a relatively lower incidence of esophageal adenocarcinoma [50].

Quercetin is thought to facilitate lipolysis in adipocytes, which can further cause cell apoptosis [52]. Animal studies lead to hypothesis that a diet rich in combined intake of these three phytochemicals might exert antitumor properties based on this synergistic effect on the downregulation of adipogenesis and further facilitation of cell death [53]. A 2013 case-controlled study in Sweden consisted of 181 patients of esophageal adenocarcinoma, 158 cases of esophageal squamous cell carcinoma, 255 cases of gastroesophageal junctional (GEJ) carcinoma, and 806 control cases [50]. The study assessed the intake of lignans, quercetin, and resveratrol in the study population by using simplified dietary pattern in quintiles. A diet rich in lignans, quercetin, and resveratrol has been characterized by the high intake of lettuce, wine, tea, tomatoes, and whole-grain bread and a low intake of milk [50]. The study demonstrated a dose-dependent correlation between the dietary score and all varieties of esophageal cancers. The adjusted odds ratio (OR) for the types of cancer was as follows: OR 0–24 for esophageal adenocarcinoma, OR 0–31 for squamous cell cancer, and OR 0–49 for gastroesophageal junction cancer [50]. The positive results of the study demonstrate that a diet high in lignans, quercetin, and resveratrol may have a protective effect in the incidence of esophageal cancer in the Swedish people [50].

7 Pharmacologic Agents Used in the Treatment of Esophageal Cancer (Table 8.1)

7.1 Tyrosine Kinase Inhibitors (TKIs)

Receptor tyrosine kinases (RTKs) are transmembrane glycoproteins that comprise three parts: an extracellular domain for ligand attachment, a transmembrane domain, and a tyrosine kinase motif [54, 55]. The extracellular domain of the RTK helps in the identification of various subfamilies of the kinases. Binding of the corresponding ligands to the RTKs results in their activation via phosphorylation of tyrosine residues on the receptor and through intracellular signaling proteins [56]. The activated RTKs play an important role in the regulation of many cellular processes, such as cellular proliferation, adhesion, differentiation, migration, and survival [57]. RTKs are classified into at least 21 groups, such as the vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), and platelet-derived growth factor receptor

Table 8.1 Summary of a select group of pharmacologic agents used in the treatment of esophageal cancer

Sl. No.	Study authors (year)	Drug tested	Phase of the study	Study population	Clinical outcomes
EGFR inhibitors					
1.	Dutton et al. (2014)	Gefitinib	Phase III	Patients with esophageal cancer progression after chemotherapy	In all the patients, gefitinib as a second-line therapy did not improve the overall survival
2.	Zhai et al. (2010)	Erlotinib	Phase II pilot study	Concurrent erlotinib and radiation therapy in patients intolerant to chemoradiotherapy	Erlotinib + radiotherapy was effective and tolerable in esophageal squamous cell carcinoma patients
3.	Huang et al. (2016)	Icotinib	Phase II	Patients with pretreated advanced esophageal squamous cell cancer and EGFR overexpression	Icotinib showed positive results in terms of overall survival and progression-free survival
VEGFR inhibitors					
4.	Horgan et al. (2016)	Sunitinib	Phase II	Patients who underwent chemoradiotherapy and surgery for locally advanced esophageal cancer	Adjuvant sunitinib resulted in median survival of 26 months and a 2-year survival rate of 52%
5.	Janjigan et al. (2015)	Sorafenib	Phase II	Patients with chemotherapy-refractory esophageal carcinoma	In all the patients, the median overall survival was 9.7 months and median progression-free survival was 3.6 months

(PDGFR) families [58]. In cancer cells, multiple signaling processes including cellular proliferation, differentiation, and metabolic pathways are activated by dimerization of RTK. Studies have shown that monoclonal antibodies can inhibit the activation and overexpression of kinases in cancer cells. Some of the RTK inhibitors that have been approved by regulatory agencies for the treatment of cancers include trastuzumab for advanced-stage breast cancer [59], gefitinib used in the treatment of non-small cell lung carcinoma [60], and cetuximab for metastatic colon cancer [61]. The benefits of targeted therapy in esophageal cancer are rather limited. The application of molecular targeted drugs is also rather limited in esophageal cancer, and is restricted to the inhibition of EGFR, VEGFR, or HER-2.

8 EGFR Inhibitors

The EGFR is a tyrosine kinase receptor that helps in cell growth, cell differentiation, migration of cells, and metastasis. Studies have shown that EGFR overexpression is noticed in about 30–90% of esophageal cancers [62]. A 2004 study in patients diagnosed with esophageal cancer has shown a correlation between the EGFRs and overall survival (OS) [63]. In that study, the median OS was 16 months in the EGFR-positive cases whereas the median OS was 35 months in the EGFR-negative patients [63]. This signifies the importance of targeting EGFR in esophageal cancer, and to that aim, various drugs have been tested such as cetuximab, panitumumab, and gefitinib. Cetuximab has shown survival benefits in different malignancies such as cancers such as colon cancer and head-and-neck cancers, when combined with chemotherapy [64]. Unfortunately, it failed to produce any positive results in esophageal cancer. Since the year 2010, many clinical trials have been conducted regarding the efficacy of cetuximab and a meta-analysis including ten trials has shown that cetuximab combined with chemotherapy did not have any appreciable survival benefits in either local or advanced esophageal cancer [65]. Panitumumab is another EGFR inhibitor that also failed to show improvement in overall survival in phase III clinical trials [66]. Similarly, gefitinib and nimotuzumab were tested for esophageal cancer, but these agents also failed to demonstrate any positive outcomes in phase III trials [67, 68].

9 VEGFR Inhibitors

The VEGFRs play major role(s) in tumor angiogenesis, which helps in cancer cell invasion and metastasis. Studies have demonstrated that up to 30–60% of advanced esophageal cancer cases have upregulation of VEGFR [69]. Ramucirumab, a VEGFR/HER2 inhibitor, when used as a second-line monotherapy showed promising results in gastric cancer, including gastroesophageal junction carcinoma. The HER2 receptor is upregulated in 20% of esophageal cancers. Ramucirumab is FDA approved as second-line therapy of advanced esophageal cancer, either as a single agent or when used with abraxane [70]. Similarly, trastuzumab, another HER2 inhibitor, has also been approved for the first-line treatment of esophageal cancer in combination with chemotherapy [71]. Apatinib, a VEGFR/HER2 inhibitor, has shown positive results in terms of overall survival as well as progression-free survival in comparison with placebo in the Asian patients with advanced GE junction cancer [72].

10 Immunotherapy

Immunotherapies act by boosting the body's innate immune response by enabling destruction of tumor cells. Cytotoxic cluster differentiation (CD) 8 T cells recognize and destroy cancer cells through apoptosis. When cancer cells undergo mutation, they develop immunosuppressive mechanisms that either inhibit or anergize cytotoxic T cells [73]. Below we summarize some of the key immunotherapeutic studies related to esophageal and related cancers.

10.1 Immune Checkpoint Inhibitors

Programmed cell death protein 1 (PD-1) is an immune checkpoint-signaling molecule, which functions as an inhibitory signaling receptor on T-lymphocytes. Studies have demonstrated that tumor cells have overexpression of programmed cell death-ligand 1 (PD-L1) that helps in the suppression of lymphocyte activation and further cell destruction by T cells [74]. Targeting PD-L1 or PD-1 has demonstrated benefits in the treatment of various cancers such as lymphomas, lung, melanoma, head and neck, and some gynecologic malignancies [73]. Studies have shown that the majority of esophageal cancers present with *p53* gene mutations presumably due to the impact of chronic gastroesophageal reflux and inflammation resulting in continuing cell turnover, eventually resulting in tumorigenesis [75]. Furthermore, PD-L1 is detected in around 40% of the GEJ adenocarcinomas and esophageal adenocarcinomas, thus making them vulnerable to the checkpoint inhibitor therapies [76].

10.2 Pembrolizumab

Pembrolizumab is a monoclonal antibody that aims to inhibit PD-1. A phase Ib trial consisting of 39 patients (KEYNOTE-012) [77] was conducted to assess the effects of pembrolizumab as a first-line medication in metastatic or recurrent gastric and GEJ PD-L1-positive adenocarcinomas. In that study, pembrolizumab showed positive results in terms of objective response rate (ORR) (22%) and OS (11.4 months), and 12-month survival rate (42%) [77].

10.3 Nivolumab

Nivolumab is a monoclonal antibody that inhibits PD-1. It was evaluated for metastatic GEJ and gastric cancers in a randomized, phase III trial (ATTRACTION-2) [78] that recruited patients from Asian countries including

Japan, South Korea, and Taiwan. In that study, nivolumab's overall response rate (ORR) was 11.2% with an OS of 5.3 months in comparison to 4.1 months for patients receiving placebo. In the ATTRACTION-04 phase II trial [79], the combination of nivolumab with S-1 and oxaliplatin demonstrated an ORR of 57.1%, with progression-free survival of 9.7 months, while the combination of nivolumab, capecitabine, and oxaliplatin had an ORR of 76.5% and a PFS of 10.6 months. Both combinations were tolerated well and had fewer adverse events and these combinations have been tested in a phase III trial. Nivolumab has been approved for patients with PD-L1-positive GE junction and gastric cancer in Japan. This is expected to receive approval for esophageal cancer therapy. Another study (CheckMate 032) [80] assessed nivolumab in 160 patients with metastatic esophagogastric or advanced cancer refractory to chemotherapy. The study showed a 12% ORR and a 1-year survival rate of 39%, with a median OS of around 7 months for nivolumab alone [80]. Interestingly, the study also concluded that the PD-L1 status did not have a significant association with the antitumor response.

10.4 Avelumab

Avelumab is an anti-PD-L1 monoclonal antibody. A phase III trial (JAVELIN 300) [81] evaluated the potential of avelumab in advanced gastric and GEJ cancers that was refractory to chemotherapy. Unfortunately, results from this trial were discouraging as the ORR for avelumab was worse than that from the treatment with paclitaxel (4% vs. 8%) when considered as a third-line treatment option [81].

10.5 Durvalumab

Durvalumab is a high-affinity, selective human IgG1κ monoclonal antibody that functions by blocking PD-L1 binding to CD80 and PD-1. Studies utilizing a dose of 10 mg/kg of durvalumab administered intravenously biweekly for 12 months can have a positive impact on gastroesophageal cancers [82]. A phase II open-label study consisting of 23 patients is investigating treatment with 1500 mg of maintenance durvalumab offered intravenously every 4 weeks to patients with persistent residual esophageal cancer after definitive surgery following concurrent chemoradiation (NCT02639065). Another ongoing study consists of a phase Ib/II study on GEJ or gastric adenocarcinoma patients in the second- and third-line metastatic settings for treatment with durvalumab alone, single-agent tremelimumab, or combination therapy with durvalumab and tremelimumab [anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein 4)] [83].

11 Combination Drugs

The CTLA-4 is a receptor located on the surface of T cells. Attachment of CTLA-4 to CD80 or CD86 results in downregulation of immune system. Ipilimumab, the powerful anti-CTLA-4 drug, failed to show any benefits when used alone in advanced gastric or GEJ adenocarcinomas when compared to best supportive care (BSC) [84]. This poor response was also demonstrated by another phase II trial, this time using a different anti-CTLA-4 monoclonal antibody (i.e., tremenumab) that was tried as a second-line treatment for metastatic gastric and esophageal adenocarcinoma [85]. Combination therapy consisting of anti-PD-1 (nivolumab) and anti-CTLA-4 (ipilimumab) checkpoint inhibitors has shown efficacy in phase I and phase II studies and this combination is currently being evaluated in a phase III trial [86].

A non-randomized study, KEYNOTE-059 [87], assessed the efficacy of pembrolizumab as a third-line therapy in patients with advanced and chemotherapy-refractory gastric and GEJ adenocarcinomas. In that study, the ORR was 11.6% for all patients. Interestingly, the drug efficacy was dependent on the PD-L1 status; the ORR for the PD-L1-positive cases was 15.5% whereas it was only 6.4% for the PD-L1-negative cases. Furthermore, the combination of pembrolizumab with chemotherapeutic agents (i.e., cisplatin plus 5-FU or capecitabine) resulted in an overall response rate of 60% for all patients, with PD-L1-positive cases again displaying higher ORR compared to the PD-L1-negative cases (69% vs. 38%). Additionally, when the single-agent pembrolizumab was used as a first-line treatment in patients with PD-L1-positive status, the ORR was 26%, which was considered promising [88]; however, the medication had significant adverse effects. Based on the results of the KEYNOTE-059 trial, pembrolizumab was approved by the FDA as a third-line option for PD-L1-positive, metastatic, or locally advanced gastric and GEJ adenocarcinomas [89]. Contrary to the above results, a phase III randomized trial (KEYNOTE-061) [90] compared the efficacy of pembrolizumab with paclitaxel in patients with advanced gastric and GEJ cancer and a positive PD-L1 status. In that study, pembrolizumab did not show any positive results. This finding suggested that the PD-L1 status may not serve as a reliable prognostic biomarker for making ideal treatment choices.

Other recent trials on the efficacy of pembrolizumab in PD-L1-positive esophageal squamous cell cancers include the KEYNOTE-180 phase II and KEYNOTE-181 phase III trials. Pembrolizumab showed positive response in metastatic ESC patients who underwent >2 lines of standard therapy, in terms of the ORR (14.3%). For esophageal adenocarcinoma, the results were more evident in those with positive PD-L1 status (13.8% vs. 6.3%) [91]. Later, the KEYNOTE-181 trial demonstrated that pembrolizumab when used in metastatic ESC as a second-line treatment resulted in a slightly improved OS when compared to chemotherapy, but this effect was not found to be statistically significant [92]. In July 2019, pembrolizumab received FDA approval as a second-line agent for the PD-L1-positive ESC. In addition, these results have paved the way for further trials that worked on analyzing the

combination of pembrolizumab and chemotherapy as a first-line treatment of advanced esophageal cancer. Recently, a phase II trial analyzed the effects of pembrolizumab in combination with trastuzumab, capecitabine, and oxaliplatin as the first-line therapy for EAC. The study demonstrated positive results in terms of ORR (83%) and progression-free survival (11.4 months) in subjects with metastatic esophageal adenocarcinoma and positive HER-2 status [93].

12 Conclusions and Future Perspectives

Despite the ever-growing list of phytochemicals as potential novel anticancer agents, further conclusive studies are needed to strengthen their beneficial role(s) in the management of esophageal cancer. The lack of control groups and relatively small sample sizes are some of the issues that need to be addressed in future studies. Although the molecular mechanisms behind the functions of many phytochemicals have successfully been identified, much more needs to be done in identifying the pharmacokinetics, interactions, and side effect profiles of these substances. It can be deduced from the current evidence that phytochemicals still have a long way to go before ever being formally inducted as treatment options for cancers. Even their role (s) in the prevention of cancers, at the moment, remains somewhat questionable given the low concentration and possibly inactive forms of most of these compounds in natural dietary sources. However, based on the studies conducted so far, the initial results are indeed promising and warrant further translational studies that may become more effectively implemented in clinical practice.

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References

1. Accessed March 3, 2020 from https://www.wcrf.org/dietandcancer/cancer-trends/oesophageal-cancer-statistics.
2. van Hagen, P., Hulshof, M. C., van Lanschot, J. J., Steyerberg, E. W., van Berge, et al. (2012). Preoperative chemoradiotherapy for esophageal or junctional cancer. *The New England Journal of Medicine, 366*(22), 2074–2084.
3. Kato, H., & Nakajima, M. (2013). Treatments for esophageal cancer: A review. *General Thoracic and Cardiovascular Surgery, 61*(6), 330–335.
4. Zhang, Y. (2013). Epidemiology of esophageal cancer. *World Journal of Gastroenterology, 19* (34), 5598–5606.

5. Cesas, A., & Bagajevas, A. (2004). Combined treatment of esophageal cancer: A review. *Medicina (Kaunas, Lithuania), 40*.
6. Lee, M. T., Lin, W. C., Yu, B., & Lee, T. T. (2017). Antioxidant capacity of phytochemicals and their potential effects on oxidative status in animals: A review. *Asian-Australasian Journal of Animal Sciences, 30*(3), 299–308.
7. Zhu, F., Du, B., & Xu, B. (2018). Anti-inflammatory effects of phytochemicals from fruits, vegetables, and food legumes: A review. *Critical Reviews in Food Science and Nutrition, 58*(8), 1260–1270.
8. Wang, H., Khor, T. O., Shu, L., Su, Z., Fuentes, F., Lee, J. J.-H., & Kong, A.-N. T. (2012). Plants against cancer: A review on natural phytochemicals in preventing and treating cancers and their druggability. *Anti-Cancer Agents in Medicinal Chemistry, 12*(10), 1281–1305.
9. Dutt, R., Garg, V., Khatri, N., & Madan, A. K. (2019). Phytochemicals in anticancer drug development. *Anti-Cancer Agents in Medicinal Chemistry, 19*(2), 172–183.
10. Liu, R. H. (2004). Potential synergy of phytochemicals in cancer prevention: Mechanism of action. *The Journal of Nutrition, 134*(12 Suppl), 3479S–3485S.
11. Chung, M.-Y., Lim, T. G., & Lee, K. W. (2013). Molecular mechanisms of chemopreventive phytochemicals against gastroenterological cancer development. *World Journal of Gastroenterology, 19*(7), 984–993.
12. Wargovich, M. J. (1997). Experimental evidence for cancer preventive elements in foods. *Cancer Letters, 114*(1-2), 11–17.
13. Phytochemicals directory. Accessed March 3, 2020 from https://www.phytochemicals.info/phytochemicals/curcumin.php.
14. Shehzad, A., Wahid, F., & Lee, Y. S. (2010). Curcumin in cancer chemoprevention: Molecular targets, pharmacokinetics, bioavailability, and clinical trials. *Archiv der Pharmazie (Weinheim), 343*(9), 489–499.
15. Anand, P., Sundaram, C., Jhurani, S., Kunnumakkara, A. B., & Aggarwal, B. B. (2008). Curcumin and cancer: An 'old-age' disease with an 'age-old' solution. *Cancer Letters, 267*(1), 133–164.
16. Lee, K. W., Bode, A. M., & Dong, Z. (2011). Molecular targets of phytochemicals for cancer prevention. *Nature Reviews. Cancer, 11*(3), 211–218.
17. Guo, Y., Shu, L., Zhang, C., Su, Z. Y., & Kong, A. N. (2015). Curcumin inhibits anchorage-independent growth of HT29 human colon cancer cells by targeting epigenetic restoration of the tumor suppressor gene DLEC1. *Biochemical Pharmacology, 94*(2), 69–78.
18. Almanaa, T. N., Geusz, M. E., & Jamasbi, R. J. (2012). Effects of curcumin on stem-like cells in human esophageal squamous carcinoma cell lines. *BMC Complementary and Alternative Medicine, 12*, 195.
19. Sullivan-Coyne, G., Sullivan, G. C., Donovan, T. R., Piwocka, K., & McKenna, S. L. (2009). Curcumin induces apoptosis-independent death in oesophageal cancer cells. *British Journal of Cancer, 101*(9), 1585–1595.
20. Pendleton, E. G., Jamasbi, R. J., & Geusz, M. E. (2019). Tetrahydrocurcumin, curcumin, and 5-fluorouracil effects on human esophageal carcinoma cells. *Anti-Cancer Agents in Medicinal Chemistry, 19*(8), 1012–1020.
21. Valko, M., Rhodes, C. J., Moncol, J., Izakovic, M., & Mazur, M. (2006). Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chemico-Biological Interactions, 160*(1), 1–40.
22. Bower, M. R., Aiyer, H. S., Li, Y., & Martin, R. C. G. (2010). Chemoprotective effects of curcumin in esophageal epithelial cells exposed to bile acids. *World Journal of Gastroenterology, 16*(33), 4152–4158.
23. Rawat, N., Alhamdani, A., McAdam, E., Cronin, J., Eltahir, Z., Lewis, P., Griffiths, P., Baxter, J. N., & Jenkins, G. J. (2012). Curcumin abrogates bile-induced NF-κB activity and DNA damage in vitro and suppresses NF-κB activity whilst promoting apoptosis in vivo, suggesting chemopreventative potential in Barrett's oesophagus. *Clinical & Translational Oncology, 14*(4), 302–311.

24. Liao, S., Xia, J., Chen, Z., Zhang, S., Ahmad, A., Miele, L., Sarkar, F. H., & Wang, Z. (2011). Inhibitory effect of curcumin on oral carcinoma CAL-27 cells via suppression of Notch-1 and NF-κB signaling pathways. *Journal of Cellular Biochemistry, 112*(4), 1055–1065.
25. Masuda, S. (2012). Dysfunctional transforming growth factor-β signaling with constitutively active notch signaling in Barrett's esophageal adenocarcinoma. *Cancer, 118*(7), 1956–1957.
26. Haraguchi, N., Utsunomiya, T., Inoue, H., Tanaka, F., Mimori, K., Barnard, G. F., & Mori, M. (2006). Characterization of a side population of cancer cells from human gastrointestinal system. *Stem Cells, 24*(3), 506–513.
27. Ricci-Vitiani, L., Lombardi, D. G., Pilozzi, E., Biffoni, M., Todaro, M., Peschle, C., & De Maria, R. (2007). Identification and expansion of human colon-cancer-initiating cells. *Nature, 445*(7123), 111–115.
28. D'Angelo, R. C., & Wicha, M. S. (2010). Stem cells in normal development and cancer. *Progress in Molecular Biology and Translational Science, 95*, 113–158.
29. Dean, M., Fojo, T., & Bates, S. (2005). Tumour stem cells and drug resistance. *Nature Reviews. Cancer, 5*(4), 275–284.
30. Chacko, S. M., Thambi, P. T., Kuttan, R., & Nishigaki, I. (2010). Beneficial effects of green tea: A literature review. *Chinese Medicine, 5*, 13.
31. Fujiki, H., Watanabe, T., Sueoka, E., Rawangkan, A., & Suganuma, M. (2018). Cancer prevention with green tea and its principal constituent, EGCG: From early investigations to current focus on human cancer stem cells. *Molecules and Cells, 41*(2), 73–82.
32. Wang, L. X., Shi, Y. L., Zhang, L. J., Wang, K. R., Xiang, L. P., Cai, Z. Y., et al. (2019). Inhibitory effects of (−)-Epigallocatechin-3-gallate on esophageal cancer. *Molecules, 8*, 24(5).
33. Khan, N., Afaq, F., Saleem, M., Ahmad, N., & Mukhtar, H. (2006). Targeting multiple signaling pathways by green tea polyphenol (−)-epigallocatechin-3-gallate. *Cancer Research, 66*(5), 2500–2505.
34. Singh, B. N., Shankar, S., & Srivastava, R. K. (2011). Green tea catechin, epigallocatechin-3-gallate (EGCG): Mechanisms, perspectives and clinical applications. *Biochemical Pharmacology, 82*(12), 1807–1821.
35. Ye, F., Zhang, G.-H., Guan, B.-X., & Xu, X.-C. (2012). Suppression of esophageal cancer cell growth using curcumin, (−)-epigallocatechin-3-gallate and lovastatin. *World Journal of Gastroenterology, 18*(2), 126–135.
36. Li, Z. G., Shimada, Y., Sato, F., Maeda, M., Itami, A., Kaganoi, J., et al. (2002). Inhibitory effects of epigallocatechin-3-gallate on N-nitrosomethylbenzylamine-induced esophageal tumorigenesis in F344 rats. *International Journal of Oncology, 21*(6), 1275–1283.
37. Hou, Z., Sang, S., You, H., Lee, M. J., Hong, J., Chin, K. V., & Yang, C. S. (2005). Mechanism of action of (−)-epigallocatechin-3-gallate: Auto-oxidation-dependent inactivation of epidermal growth factor receptor and direct effects on growth inhibition in human esophageal cancer KYSE 150 cells. *Cancer Research, 65*(17), 8049–8056.
38. Ge, X. X., Xing, M. Y., Yu, L. F., & Shen, P. (2013). Carotenoid intake and esophageal cancer risk: A meta-analysis. *Asian Pacific Journal of Cancer Prevention, 14*(3), 1911–1918.
39. Zhou, H.-B., Yan, Y., Sun, Y.-N., & Zhu, J.-R. (2003). Resveratrol induces apoptosis in human esophageal carcinoma cells. *World Journal of Gastroenterology, 9*(3), 408–411.
40. Stoner, G. D., Kresty, L. A., Carlton, P. S., Siglin, J. C., & Morse, M. A. (1999). Isothiocyanates and freeze-dried strawberries as inhibitors of esophageal cancer. *Toxicological Sciences, 52* (2 Suppl), 95–100.
41. Adlercreutz, H. (2007). Lignans and human health. *Critical Reviews in Clinical Laboratory Sciences, 44*(5-6), 483–525.
42. Hertog, M. G., Hollman, P. C., & Katan, M. B. (1992). Content of potentially anticarcinogenic flavonoids of 28 vegetables and 9 fruits commonly consumed in the Netherlands. *Journal of Agricultural and Food Chemistry, 40*(12), 2379–2383.
43. Peters, P. H., Slimani, N., van der Schouw, Y. T., Grace, P. B., Navarro, C., Tjonneland, A., Olsen, A., Clavel-Chapelon, F., Touillaud, M., Boutron-Ruault, M. C., & Jenab, M. (2007).

Variations in plasma phytoestrogen concentrations in European adults. *The Journal of Nutrition, 137*(5), 1294–1300.
44. Lamuela-Raventos, R. M., Romero-Perez, A. I., Waterhouse, A. L., & de la Torre-Boronat, M. C. (1995). Direct HPLC analysis of cis-and trans-resveratrol and piceid isomers in Spanish red Vitis vinifera wines. *Journal of Agricultural and Food Chemistry, 43*(2), 281–283.
45. Penttinen, P., Jaehrling, J., Damdimopoulos, A. E., Inzunza, J., Lemmen, J. G., van der Saag, P., Pettersson, K., Gauglitz, G., Mäkelä, S., & Pongratz, I. (2007). Diet-derived polyphenol metabolite enterolactone is a tissue-specific estrogen receptor activator. *Endocrinology, 148* (10), 4875–4886.
46. van der Woude, H., ter Veld, M. G., Jacobs, N., van der Saag, P. T., Murk, A. J., & Rietjens, I. M. (2005). The stimulation of cell proliferation by quercetin is mediated by the estrogen receptor. *Molecular Nutrition & Food Research, 49*(8), 763–771.
47. Gehm, B. D., McAndrews, J. M., Chien, P. Y., & Jameson, J. L. (1997). Resveratrol, a polyphenolic compound found in grapes and wine, is an agonist for the estrogen receptor. *Proceedings of the National Academy of Sciences of the United States of America, 94*(25), 14138–14143.
48. Tiffin, N., Suvarna, S. K., Trudgill, N. J., & Riley, S. A. (2003). Sex hormone receptor immunohistochemistry staining in Barrett's oesophagus and adenocarcinoma. *Histopathology, 42*(1), 95–96.
49. Lagergren, J., & Lagergren, P. (2013). Recent developments in esophageal adenocarcinoma. *CA: A Cancer J Clin, 63*(4), 232–248.
50. Lin, Y., Yngve, A., Lagergren, J., & Lu, Y. (2014). A dietary pattern rich in lignans, quercetin and resveratrol decreases the risk of oesophageal cancer. *The British Journal of Nutrition, 112* (12), 2002–2009.
51. Tavani, A., Bertuzzi, M., Talamini, R., Gallus, S., Parpinel, M., Franceschi, S., Levi, F., & La Vecchia, C. (2003). Coffee and tea intake and risk of oral, pharyngeal and esophageal cancer. *Oral Oncology, 39*(7), 695–700.
52. Kuppusamy, U. R., & Das, N. P. (1994). Potentiation of β-adrenoceptor agonist-mediated lipolysis by quercetin and fisetin in isolated rat adipocytes. *Biochemical Pharmacology, 47* (3), 521–529.
53. Park, H. J., Yang, J. Y., Ambati, S., Della-Fera, M. A., Hausman, D. B., Rayalam, S., & Baile, C. A. (2008). Combined effects of genistein, quercetin, and resveratrol in human and 3T3-L1 adipocytes. *Journal of Medicinal Food, 11*(4), 773–783.
54. Robinson, D. R., Wu, Y. M., & Lin, S. F. (2000). The protein tyrosine kinase family of the human genome. *Oncogene, 19*(49), 5548–5557.
55. Schlessinger, J. (2000). Cell signaling by receptor tyrosine kinases. *Cell, 103*(2), 211–225.
56. Morishita, A., Gong, J., & Masaki, T. (2014). Targeting receptor tyrosine kinases in gastric cancer. *World Journal of Gastroenterology, 20*(16), 4536.
57. Hubbard, S. R., & Till, J. H. (2000). Protein tyrosine kinase structure and function. *Annual Review of Biochemistry, 69*(1), 373–398.
58. Becker, J. C., Müller-Tidow, C., Serve, H., Domschke, W., & Pohle, T. (2006). Role of receptor tyrosine kinases in gastric cancer: New targets for a selective therapy. *World Journal of Gastroenterology, 12*(21), 3297–3305.
59. Shawver, L. K., Slamon, D., & Ullrich, A. (2002). Smart drugs: Tyrosine kinase inhibitors in cancer therapy. *Cancer Cell, 1*(2), 117–123.
60. Cohen, M. H., Williams, G. A., Sridhara, R., Chen, G., & Pazdur, R. (2003). FDA drug approval summary: Gefitinib (ZD1839) (Iressa) tablets. *The Oncologist, 8*(4), 303–306.
61. (2004). New treatments for colorectal cancer. *FDA Consumer, 38*(3), 17.
62. Al-Kasspooles, M., Moore, J. H., Orringer, M. B., & Beer, D. G. (1993). Amplification and over-expression of the EGFR and erbB-2 genes in human esophageal adenocarcinomas. *International Journal of Cancer, 54*(2), 213–219.
63. Wilkinson, N. W., Black, J. D., Roukhadze, E., Driscoll, D., Smiley, S., Hoshi, H., Geradts, J., Javle, M., & Brattain, M. (2004). Epidermal growth factor receptor expression correlates with

histologic grade in resected esophageal adenocarcinoma. *Journal of Gastrointestinal Surgery, 8* (4), 448–453.
64. Tew, W. P., Kelsen, D. P., & Ilson, D. H. (2005). Targeted therapies for esophageal cancer. *The Oncologist, 10*(8), 590–601.
65. Huang, Z. H., Ma, X. W., Zhang, J., Li, X., Lai, N. L., & Zhang, S. X. (2018). Cetuximab for esophageal cancer: An updated meta-analysis of randomized controlled trials. *BMC Cancer, 18* (1), 1170.
66. Waddell, T., Chau, I., Cunningham, D., Gonzalez, D., Okines, A. F., Wotherspoon, A., Saffery, C., Middleton, G., Wadsley, J., Ferry, D., & Mansoor, W. (2013). Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): A randomized, open-label phase 3 trial. *The Lancet Oncology, 14*(6), 481–489.
67. Dutton, S. J., Ferry, D. R., Blazeby, J. M., Abbas, H., Dahle-Smith, A., Mansoor, W., Thompson, J., Harrison, M., Chatterjee, A., Falk, S., & Garcia-Alonso, A. (2014). Gefitinib for oesophageal cancer progressing after chemotherapy (COG): A phase 3, multicentre, double-blind, placebo-controlled randomized trial. *The Lancet Oncology, 15*(8), 894–904.
68. Zhang, X., Jia, J., Lu, M., Wang, X., Gong, J., Li, J., Li, J., Li, Y., Zhang, X., Lu, Z., et al. (2017). Nimotuzumab plus paclitaxel and cisplatin as 1st line treatment for unresectable esophageal squamous cell carcinoma: Long term follow-up of survival in a phase II study. *Journal of Clinical Oncology, 35*, e15573.
69. Kleespies, A., Guba, M., Jauch, K. W., & Bruns, C. J. (2004). Vascular endothelial growth factor in esophageal cancer. *Journal of Surgical Oncology, 87*(2), 95–104.
70. Fuchs, C. S., Shitara, K., Di Bartolomeo, M., Lonardi, S., Al-Batran, S. E., Van Cutsem, E., Ilson, D. H., Alsina, M., Chau, I., Lacy, J., & Ducreux, M. (2019). Ramucirumab with cisplatin and fluoropyrimidine as first-line therapy in patients with metastatic gastric or junctional adenocarcinoma (RAINFALL): A double-blind, randomised, placebo-controlled, phase 3 trial. *The Lancet Oncology, 20*(3), 420–435.
71. Creemers, A., Ebbing, E. A., Hooijer, G. K., Stap, L., Jibodh-Mulder, R. A., Gisbertz, S. S., van Berge Henegouwen, M. I., van Montfoort, M. L., Hulshof, M. C., Krishnadath, K. K., & van Oijen, M. G. (2018). The dynamics of HER2 status in esophageal adenocarcinoma. *Oncotarget, 9*(42), 26787.
72. Li, J., Qin, S., Xu, J., Xiong, J., Wu, C., Bai, Y., Liu, W., Tong, J., Liu, Y., Xu, R., & Wang, Z. (2016). Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. *Journal of Clinical Oncology, 34*(13), 1448–1454.
73. Barsouk, A., Rawla, P., Hadjinicolaou, A. V., Aluru, J. S., & Barsouk, A. (2019). Targeted therapies and immunotherapies in the treatment of esophageal cancers. *Medical Science, 7*(10), 100.
74. Sharpe, A. H., & Pauken, K. E. (2018). The diverse functions of the PD-1 inhibitory pathway. *Nature Reviews. Immunology, 18*(3), 153.
75. Kailasam, A., Mittal, S. K., & Agrawal, D. K. (2015). Epigenetics in the pathogenesis of esophageal adenocarcinoma. *Clinical and Translational Science, 8*(4), 394–402.
76. Raufi, A. G., & Klempner, S. J. (2015). Immunotherapy for advanced gastric and esophageal cancer: Pre-clinical rationale and ongoing clinical investigations. *Journal of Gastrointestinal Oncology Journal of Gastrointestinal Oncology, 6*(5), 561–569.
77. Muro, K., Chung, H. C., Shankaran, V., Geva, R., Catenacci, D., Gupta, S., Eder, J. P., Golan, T., Le, D. T., Burtness, B., & McRee, A. J. (2016). Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): A multicentre, open-label, phase 1b trial. *The Lancet Oncology, 17*(6), 717–726.
78. Kang, Y. K., Boku, N., Satoh, T., Ryu, M. H., Chao, Y., Kato, K., Chung, H. C., Chen, J. S., Muro, K., Kang, W. K., & Yeh, K. H. (2017). Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous

chemotherapy regimens (ONO-4538-12, ATTRACTION-2): A randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet, 390*(10111), 2461–2471.
79. Boku, N., Ryu, M. H., Kato, K., Chung, H. C., Minashi, K., Lee, K. W., Cho, H., Kang, W. K., Komatsu, Y., Tsuda, M., & Yamaguchi, K. (2019). Safety and efficacy of nivolumab in combination with S-1/capecitabine plus oxaliplatin in patients with previously untreated, unresectable, advanced, or recurrent gastric/gastroesophageal junction cancer: Interim results of a randomized, phase II trial (ATTRACTION-4). *Annals of Oncology, 30*(2), 250–258.
80. Le, D. T., Bendell, J. C., Calvo, E., Kim, J. W., Ascierto, P. A., Sharma, P., Ott, P. A., Bono, P., Jaeger, D., Evans, T. J., & De Braud, F. G. (2016). Safety and activity of nivolumab monotherapy in advanced and metastatic (A/M) gastric or gastroesophageal junction cancer (GC/GEC): Results from the CheckMate-032 study. *Journal of Clinical Oncology, 21*, 34(6).
81. Bang, Y. J., Ruiz, E. Y., Van Cutsem, E., Lee, K. W., Wyrwicz, L., Schenker, M., Alsina, M., Ryu, M. H., Chung, H. C., Evesque, L., & Al-Batran, S. E. (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. *Annals of Oncology, 29*(10), 2052–2060.
82. Segal, N. H., Antonia, S. J., Brahmer, J. R., Maio, M., Blake-Haskins, A., Li, X., Vasselli, J., Ibrahim, R. A., Lutzky, J., & Khleif, S. (2014). Preliminary data from a multi-arm expansion study of MEDI4736, an anti-PD-L1 antibody. *Journal of Clinical Oncology, 32*(suppl; Abstr 3002), 5s.
83. Kelly, R. J., Chung, K., Gu, Y., Steele, K. E., Rebelatto, M. C., Robbins, P. B., Tavakkoli, F., Karakunnel, J. J., Lai, D. W., & Almhanna, K. (2015). Phase Ib/II study to evaluate the safety and antitumor activity of durvalumab (MEDI4736) and tremelimumab as monotherapy or in combination, in patients with recurrent or metastatic gastric/gastroesophageal junction adenocarcinoma. *Journal for Immunotherapy of Cancer, 3*(Suppl 2), 157.
84. Bang, Y. J., Cho, J. Y., Kim, Y. H., Kim, J. W., Di Bartolomeo, M., Ajani, J. A., Yamaguchi, K., Balogh, A., Sanchez, T., & Moehler, M. (2017). Efficacy of sequential ipilimumab monotherapy versus best supportive care for unresectable locally advanced/metastatic gastric or gastroesophageal junction cancer. *Clinical Cancer Research, 23*(19), 5671–5678.
85. Ralph, C., Elkord, E., Burt, D. J., O'Dwyer, J. F., Austin, E. B., Stern, P. L., Hawkins, R. E., & Thistlethwaite, F. C. (2010). Modulation of lymphocyte regulation for cancer therapy: A phase II trial of tremelimumab in advanced gastric and esophageal adenocarcinoma. *Clinical Cancer Research, 16*(5), 1662–1672.
86. Janjigian, Y. Y., Bendell, J., Calvo, E., Kim, J. W., Ascierto, P. A., Sharma, P., Ott, P. A., Peltola, K., Jaeger, D., Evans, J., & De Braud, F. (2018). CheckMate-032 study: Efficacy and safety of nivolumab and nivolumab plus ipilimumab in patients with metastatic esophagogastric cancer. *Journal of Clinical Oncology, 36*(28), 2836–2844.
87. Fuchs, C. S., Doi, T., Jang, R. W., Muro, K., Satoh, T., Machado, M., Sun, W., Jalal, S. I., Shah, M. A., Metges, J. P., & Garrido, M. (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 Oncology, 4*(5), e180013.
88. Bang, Y. J., Kang, Y. K., Catenacci, D. V., Muro, K., Fuchs, C. S., Geva, R., Hara, H., Golan, T., Garrido, M., Jalal, S. I., & Borg, C. (2019). Pembrolizumab alone or in combination with chemotherapy as first-line therapy for patients with advanced gastric or gastroesophageal junction adenocarcinoma: Results from the phase II nonrandomized KEYNOTE-059 study. *Gastric Cancer, 22*(4), 828–837.
89. Fashoyin-Aje, L., Donoghue, M., Chen, H., He, K., Veeraraghavan, J., Goldberg, K. B., Keegan, P., McKee, A. E., & Pazdur, R. (2019). FDA approval summary: Pembrolizumab for recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma expressing PD-L1. *The Oncologist, 24*(1), 103–109.
90. Ohtsu, A., Tabernero, J., Bang, Y. J., Fuchs, C. S., Sun, L., Wang, Z., Csiki, I., Koshiji, M., & Van Cutsem, E. (2016). Pembrolizumab (MK-3475) versus paclitaxel as second-line therapy for

advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma: Phase 3 KEYNOTE-061 study. *Journal of Clinical Oncology, 34*, TPS183.

91. Shah, M. A., Kojima, T., Hochhauser, D., Enzinger, P., Raimbourg, J., Hollebecque, A., Lordick, F., Kim, S. B., Tajika, M., Kim, H. T., & Lockhart, A. C. (2019). Efficacy and safety of pembrolizumab for heavily pretreated patients with advanced, metastatic adenocarcinoma or squamous cell carcinoma of the esophagus: The phase 2 KEYNOTE-180 study. *JAMA Oncology, 5*(4), 546–550.
92. Shah, M. A., Adenis, A., Enzinger, P. C., Kojima, T., Muro, K., Bennouna, J., Francois, E., Hsu, C. H., Moriwaki, T., Kim, S. B., & Lee, S. H. (2019). Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: Phase 3 KEYNOTE-181 study. *Journal of Clinical Oncology, 37*, 4010.
93. Kojima, T., Muro, K., Francois, E., Hsu, C.-H., Moriwaki, T., Kim, S.-B., Lee, S.-H., Bennouna, J., Kato, K., Lin, S., et al. (2019). Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: Phase III KEYNOTE-181 study. *Journal of Clinical Oncology, 37*(4 Suppl), 2. https://doi.org/10.1200/JCO.2019.37.4_suppl.2.