# Initial systemic therapy for metastatic esophageal and gastric cancer

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## INTRODUCTION

Gastric, gastroesophageal junction (GEJ), and esophageal cancers often present as advanced unresectable or metastatic disease. These advanced unresectable or metastatic cancers are not curable, and the goals of systemic therapy include palliating symptoms, improving quality of life, and prolonging overall survival (OS).

This topic will present initial systemic therapy for advanced unresectable and metastatic gastric, GEJ, and esophageal cancer. Second and later-line systemic therapy and palliative therapies for these cancers are discussed separately.

- (See "Second- and later-line systemic therapy for metastatic gastric and esophageal cancer".)
- (See "Local palliation for advanced gastric cancer".)
- (See "Endoscopic palliation of esophageal cancer".)

## HISTOLOGY, ANATOMIC DISTRIBUTION, AND EVOLUTION OF CHEMOTHERAPY STRATEGY

Together, squamous cell cancer (SCC) and adenocarcinoma account for 93 percent of all

esophageal carcinomas, but histologic and anatomic distribution has changed dramatically over the past 30 years [1]. In the 1970s, SCC accounted for approximately 70 percent of all esophageal cancers, and 22 percent of tumors were located in the upper one-third of the thoracic esophagus or in the cervical esophagus. Since the mid-1970s, the incidence of SCC in the United States has been declining steadily, while the incidence of adenocarcinoma in White male patients rose by 350 percent from 1974 to 1994. Adenocarcinoma surpassed SCC as the dominant histology in the early 1990s [2]. At the same time, there has also been a shift in the location of esophageal cancers over time. At present, 86 percent of esophageal cancers arise in the distal one-third of the thoracic esophagus, 13 percent arise in the middle third, and only 1 percent arise in the upper third or cervical esophagus. (See "Epidemiology and risk factors for esophageal cancer".)

More than 90 percent of stomach cancers are adenocarcinomas. In 1930, most cases originated in the distal stomach (gastric body and antrum ( figure 1)). Since then, the incidence of distal gastric carcinoma has declined dramatically while the incidence of adenocarcinoma of the gastroesophageal junction (GEJ) and proximal stomach has increased at a rate exceeding that of any other cancer [3]. The increasing incidence has paralleled the rise in incidence of esophageal adenocarcinoma. The term "GEJ tumor" reflects the frequent difficulty in separating the primary locations of distal esophageal and proximal gastric cancers; their natural history, response to therapy, and overall prognosis appear to be similar [4]. (See "Epidemiology of gastric cancer".)

Chemotherapy drugs that were tested for esophageal cancer at a time when SCC was the predominant histology (1970s and 1980s) were those initially developed for SCC of the head and neck, including fluorouracil (FU), cisplatin, mitomycin, methotrexate, vindesine, and bleomycin. The combination of FU plus cisplatin was adopted by many as a safe and effective standard regimen, and studies focused on the benefit of adding a third agent to the FU plus cisplatin backbone.

At the other end of the spectrum, at a time when distal gastric adenocarcinomas were the most common stomach malignancy, most regimens for advanced gastric cancer were based on FU plus an anthracycline. Cisplatin-based combinations (such as epirubicin, cisplatin, and infusional FU) were eventually shown to be superior to non-cisplatin-containing regimens and became the reference regimens for advanced gastric cancer. (See 'Epirubicin, cisplatin, and fluorouracil' below.)

Coincident with the epidemiologic changes in histologic and anatomic distribution, the treatment of advanced gastric and esophageal cancers converged, and the majority of clinical trials conducted since the mid-1990s include patients with gastric, esophageal, or GEJ cancer, regardless of histology [5,6]. Although SCCs now represent a small minority of patients enrolled in most clinical trials, histologic subtype did not appear to play a major role in response rate or survival duration in patients treated with a variety of chemotherapy regimens for metastatic esophagogastric cancer [7-12].

However, this is changing as differences in genomic alterations in biologic pathways between SCC and adenocarcinoma are beginning to be elucidated [13]. Treatment for SCC and adenocarcinoma has diverged once again with the introduction of molecularly directed therapy and immunotherapy. Therapies targeting human epidermal growth factor receptor 2 (eg, trastuzumab) and vascular endothelial growth factor (eg, ramucirumab) are applicable only to adenocarcinomas. Immunotherapy approaches using immune checkpoint inhibitors (ICIs) appear to be effective for SCC regardless of programmed cell death ligand 1 (PD-L1) expression whereas benefits in adenocarcinomas with low or absent PD-L1 expression are uncertain. (See 'Choice of therapy' below and "Second- and later-line systemic therapy for metastatic gastric and esophageal cancer", section on 'Ramucirumab with or without paclitaxel'.)

## OVERVIEW OF THE APPROACH TO FIRST-LINE THERAPY

**Goals of therapy** — The goals of chemotherapy in patients with advanced esophagogastric cancer are to palliate symptoms (including malignant dysphagia), improve quality of life, and prolong survival. A number of controlled trials and meta-analyses provide evidence for the survival benefit of palliative systemic chemotherapy for patients with advanced gastric cancer [14-20]. In one meta-analysis of three trials comparing chemotherapy with best supportive care, there was a significant benefit in overall survival (OS) in favor of chemotherapy compared with supportive care alone (hazard ratio [HR] 0.3, 95% CI 0.24-0.55), which translated into an improvement in median survival from 4.3 to 11 months [18].

**Early supportive care** — All patients with newly diagnosed advanced gastric, GEJ, or esophageal cancer should have a full assessment of symptom burden, nutritional and psychological status, and social supports as early as possible, ideally, prior to starting

systemic chemotherapy. Many patients will benefit from formal palliative care consultation and services. Early referral and initiation of interdisciplinary and palliative care services improve clinical and quality of care outcomes, including survival. (See "Benefits, services, and models of subspecialty palliative care", section on 'Rationale for palliative care'.)

Because of the anatomy, and complications from surgery or local disease progression, patients with advanced esophagogastric cancer have a high incidence of malnutrition [21,22], and psychological distress [23,24], both of which may impair survival.

Several therapeutic options are available to control symptoms of local disease progression (eg, nausea, pain, gastric outlet obstruction, bleeding), including palliative surgical resection, surgical bypass (gastrojejunostomy), radiation therapy (RT), and endoscopic techniques. Decision-making for local palliative therapy must take into account the overall prognosis of the patient in order to avoid excessive morbidity and mortality or lengthy hospital stays in those with a limited life span. (See "Local palliation for advanced gastric cancer".)

The benefit of early interdisciplinary supportive care was shown in a trial in which 328 patients with previously untreated metastatic esophagogastric cancer were randomly assigned to early interdisciplinary care with a focus on nutrition and psychological health integrated into standard oncologic care or standard care [25]. The intervention group received an interdisciplinary supportive care consultation within 14 days of initiating chemotherapy, and a follow-up consultation every three weeks thereafter. Median OS was significantly better in the early intervention group (14.8 versus 11.9, hazard ratio [HR] 0.68, 95% CI 0.51-0.9). Despite similar distribution, responses, and safety profiles of systemic therapy in the two groups, early supportive care also had a significant positive impact on emotional and cognitive functioning at week 9, and on the proportion of patients presenting with weight loss at week 9 (45 versus 58 percent).

**Choice of therapy** — We base our treatment decisions on biomarker expression and histology, as outlined in the following sections, and summarized in the algorithm (algorithm 1).

**Biomarker assessment** — Patients with advanced unresectable or metastatic gastric and esophageal cancers who are potential candidates for systemic therapy should have their tumors assessed for the following biomarkers, which are used to guide initial

management [26]:

- **All histologies:**
  - Mismatch repair deficiency (dMMR) and high levels of microsatellite instability (dMMR/MSI-H). (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Tumor MSI/IHC testing' and 'Mismatch repair deficient/MSI-H tumors' below.)
  - PD-L1 expression (ie, combined positive score [CPS] or tumor proportion score [TPS] >1 percent versus ≤1 percent). Of note, TPS may not be as predictive as CPS for PD-L1 expression in upper gastrointestinal tract adenocarcinomas [27]. (See "Principles of cancer immunotherapy", section on 'Diagnostic tests' and 'PD-L1 expression status in upper GI tract cancers' below.)
- **Gastric and GEJ adenocarcinoma:**
  - For patients who are eligible for trastuzumab, human epidermal growth factor receptor 2 (HER2) overexpression and/or gene amplification, using specific criteria developed for these tumors ( table 1 and algorithm 2). (See "Gastric cancer: Pathology and molecular pathogenesis", section on 'HER2 overexpression' and 'HER2-positive adenocarcinomas' below.)

**dMMR/MSI-H tumors** — For patients with dMMR/MSI-H metastatic esophageal and gastric cancer (either squamous cell cancer [SCC] or adenocarcinomas), the treatment approach is discussed below. (See 'Mismatch repair deficient/MSI-H tumors' below.)

**Squamous cell cancer** — For advanced SCCs, we suggest first-line therapy with chemotherapy plus immunotherapy rather than chemotherapy alone for patients with PD-L1 TPS 1+ or CPS 10+. For patients with PD-L1 TPS <1 percent or CPS <10, we also suggest chemotherapy plus immunotherapy rather than chemotherapy alone, given the generally greater activity of ICIs in SCC as compared with adenocarcinomas and a meta-analysis that suggests a significant survival benefit in this population, albeit of a lesser magnitude than for those with higher PD-L1 expression. However, in such patients, we have a lower threshold to omit or discontinue immunotherapy in the presence of unfavorable baseline features (eg, CPS <1, significant non-cancerous lung disease) or in those experiencing toxicity than we would in a patient with PD-L1 high disease given the likely lesser degree

of efficacy in this population. (See 'Squamous cell cancers' below.)

Although the chemotherapy backbone in CheckMate and KEYNOTE studies was cisplatin plus fluorouracil (FU), many clinicians, including some of the authors and editors associated with this topic review, would prefer pembrolizumab or nivolumab in combination with an oxaliplatin-based regimen such as oxaliplatin plus leucovorin with bolus plus short-term FU (FOLFOX). Where available (mainly China), camrelizumab in combination with paclitaxel and cisplatin is an appropriate alternative, as shown in the ESCORT-1st trial.

**Adenocarcinomas** — For patients with gastric and GEJ adenocarcinoma, we suggest a chemotherapy backbone including both a fluoropyrimidine and oxaliplatin, rather than other chemotherapy combinations. Options include FOLFOX ( table 2) or CAPOX/XELOX ( table 3). (See 'Combination chemotherapy' below.)

Additional therapy is guided by tumor HER2 status and level of PD-L1 expression.

- **HER2-positive adenocarcinoma** – For patients with HER2-positive adenocarcinomas, we suggest the addition of trastuzumab to chemotherapy. (See 'Trastuzumab plus chemotherapy' below.)

  Additionally, for HER2-positive cancers that also have CPS ≥1, we suggest the addition of pembrolizumab to trastuzumab and chemotherapy. (See 'Pembrolizumab plus trastuzumab and chemotherapy' below.)

  For patients who are ineligible for trastuzumab ( table 4), we offer an initial treatment approach similar to those with HER2-negative adenocarcinoma. (See 'Ineligible for trastuzumab' below.)

- **HER2-negative, PD-L1 positive, proficient MMR tumors**

  - **CPS ≥10** – For patients with HER2-negative adenocarcinoma and CPS ≥10, we suggest the addition of either nivolumab or pembrolizumab to chemotherapy, as this approach improved OS in randomized trials. (See 'CPS of 10 or more' below.)

  - **CPS 5 to less than 10** – For patients with HER2-negative adenocarcinomas and CPS of 5 to less than 10, we suggest the addition of nivolumab to chemotherapy. (See 'CPS of 5 to less than 10' below.)

- **CPS <5** – For patients with HER2-negative adenocarcinoma with CPS <5 and mismatch repair proficiency, we do not incorporate immunotherapy, given the benefits are less clear in this population and may not outweigh the risks. Such patients are treated with chemotherapy alone. (See 'CPS of less than 5' below.)

**Other adenocarcinomas and those without access to targeted therapy** — For individuals who are not receiving trastuzumab or immunotherapy first-line either because they lack a molecular biomarker or have a contraindication, intolerance, or a lack of reimbursement, the choice of chemotherapy regimen is empiric:

- In general, combination chemotherapy regimens provide higher response rates than do single agents, but this translates into only modestly longer durations of disease control and survival (measured in weeks to a few months), and a worse side effect profile. (See 'Combination chemotherapy' below and 'Is there an optimal combination regimen?' below.)

  Participation in a clinical trial is preferred. If a trial is not available, or participation is not feasible, for most patients, we suggest a fluoropyrimidine-platinum doublet rather than a triplet regimen. For most patients, we prefer an oxaliplatin-containing regimen (ie, FOLFOX ( table 2), oxaliplatin plus capecitabine, or where available, S-1 plus oxaliplatin). Other alternatives include FU plus cisplatin (or where available, S-1 plus cisplatin). (See 'Oxaliplatin combinations' below.)

  For older patients or those with a poor performance status, appropriate alternatives include leucovorin-modulated FU alone, single-agent capecitabine, single-agent irinotecan, dose-attenuated capecitabine plus oxaliplatin, or low-dose weekly taxanes. (See 'Single-agent chemotherapy' below.)

- In our view, a role for first-line ICI immunotherapy plus chemotherapy in PD-L1-negative adenocarcinomas is not yet proven, and this approach cannot be recommended. (See 'CPS of less than 5' below.)

**Response assessment** — Response is assessed using a combination of interval radiographic evaluation (typically every two to three cycles); serum tumor markers, such as carcinoembryonic antigen (if elevated at baseline); and the clinical status of the patient. Radiographic tumor response is usually quantified using Response Evaluation Criteria in Solid Tumors ( table 5) [28,29].

If tumor markers are elevated at initial evaluation, they can be serially assessed during treatment as a surrogate measure of response to therapy. While persistently rising levels of a serum tumor marker suggest disease progression, this should be confirmed with radiologic studies prior to a change in therapeutic strategy. (See "Clinical features, diagnosis, and staging of gastric cancer", section on 'Serologic markers'.)

The patient's clinical status should always be taken into consideration in combination with radiologic and tumor marker data, where patients with clinical benefit from treatment may stay on that treatment regimen despite possible radiologic progression.

**Treatment duration** — The duration of treatment in responding patients with advanced esophagogastric cancer has not been specifically studied. There are only limited data that pertain to discontinuation of a treatment regimen prior to disease progression or on modified maintenance therapy regimens. In one small randomized phase II trial that compared a "stop and go" strategy with continuous therapy following disease stabilization with first-line S-1 plus oxaliplatin, patients who continued chemotherapy beyond disease stabilization had better progression-free survival (PFS; 10.5 versus 7.2 months); however, OS and the duration of disease control were not significantly better, and quality of life was worse [30].

In general, regimens are given until the patient has progressive disease or cannot tolerate further treatment with the regimen. We recommend that each patient's treatment plan be individualized depending on tolerance and response to the treatment regimen, as well as the patient's wishes as to treatment breaks or modifications.

## EFFICACY OF INDIVIDUAL TREATMENTS

### Immunotherapy-based regimens

**PD-L1 expression status in upper GI tract cancers** — Checkpoint inhibitor immunotherapy has become a prominent and effective treatment for a variety of malignancies, but, with the exception of deficient mismatch repair (dMMR), the best way to identify the patients who are most likely to benefit is uncertain. (See 'Mismatch repair deficient/MSI-H tumors' below.)

Programmed cell death ligand 1 (PD-L1) expression is the candidate biomarker that has

been studied most extensively in trials utilizing immunotherapy that relies on programmed cell death-1 (PD-1) blockade. PD-L1 and PD-1 expression are dynamic markers that change in relation to local cytokines and other factors. Although expression of PD-L1 exists along a continuum, the thresholds that separate "positive" and "negative" PD-L1 expression remain under debate. Nevertheless, most modern trials use prespecified cutpoints, in part because compared with continuous values, the inter-pathologist agreement appears to be high [31].

Most trials with either retrospective or prospective assessments of PD-L1 status have shown trends for increased response rates to PD-1 blockade in PD-L1 "positive" tumors, as defined by prespecified cutpoints, across a variety of malignancies [32-35]. (See "Principles of cancer immunotherapy", section on 'Predictors of response to immune checkpoint inhibitors'.)

PD-L1 expression is used as a diagnostic marker in other malignancies, including upper gastrointestinal malignancies. However, the available data has been mixed. The lack of benefit for checkpoint inhibitor immunotherapy in those with low or absent PD-L1 expression has been most clearly demonstrated for adenocarcinomas while the situation for squamous cell cancers (SCCs) is evolving. Initially, results from the CheckMate 648, KEYNOTE-590, and ESCORT-1$^{st}$ trials suggested benefit for all SCC subgroups, regardless of PD-L1 expression. These data led the US Food and Drug Administration (FDA) to approve pembrolizumab, in combination with platinum- and fluoropyrimidine-based chemotherapy, for the treatment of metastatic or locally advanced esophageal or gastroesophageal junction (GEJ) carcinomas (including adenocarcinoma) with an epicenter 1 to 5 cm above the GEJ and who were not eligible for resection or chemoradiation, regardless of PD-L1 expression. However, updated analysis of the CheckMate 648 trial suggests no benefit for the addition of nivolumab to chemotherapy in esophageal SCC with a tumor proportion score (TPS) <1 percent [36]. (See 'Squamous cell cancers' below.)

There are three questions that commonly arise in this area:

- **What is the interchangeability of the assays used to assess PD-L1 expression for nivolumab versus pembrolizumab?**

  The 22C3 PharmDx IHC assay is an FDA-approved companion diagnostic assay for assessing the safety and effectiveness of pembrolizumab in a variety of malignancies, including gastric or GEJ adenocarcinoma and esophageal SCC [37]. By

contrast, the PD-L1 28-8 PharmDx assay is the approved complementary diagnostic assay for nivolumab. Data indicate that the agreement between these two assays in gastric cancer at a combined positive score (CPS) cutpoint of 1 and 10 was 96 percent [38], suggesting that they are interchangeable. Other studies suggest less concordance between the 22C3 IHC assay and the SP263 IHC assay, another commercially available PD-L1 IHC [39]. Further details on available diagnostic tests for PD-L1 are discussed separately. (See "Principles of cancer immunotherapy", section on 'Diagnostic tests'.)

- **What is the best method to score PD-L1 expression in formalin-fixed, paraffin-embedded tissue?**

  The regulatory approval of pembrolizumab for treatment of gastric and GEJ adenocarcinomas required a reproducible scoring method for use of PD-L1 protein expression as a companion diagnostic to identify likely responders to therapy. In tumors other than gastric cancer (eg, non-small cell lung cancer), the TPS (ie, the number of PD-L1-stained tumor cells divided by the total number of viable tumor cells and multiplied by 100) has been shown to identify those patients with PD-L1+ tumors who are likely to respond to pembrolizumab, but immune cell PD-L1 expression is also important. (See "Initial systemic therapy for advanced non-small cell lung cancer lacking a driver mutation", section on 'PD-L1-high tumors (at least 50 percent)'.)

  The CPS is the total number of PD-L1 stained cells (including tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells and multiplied by 100. It is a robust reproducible PD-L1 scoring method that predicts a response to pembrolizumab in gastric and GEJ cancer with inter-pathologist and intra-pathologist agreement of 97 percent, and inter-institution agreement of 92 percent [31]. This is the preferred approach. (See "Principles of cancer immunotherapy", section on 'Diagnostic tests'.)

  Nevertheless, some contemporary trials have used TPS. There are few data correlating CPS and TPS. In the CheckMate 648 trial of combined immunotherapy plus chemotherapy versus chemotherapy alone in advanced SCC, a TPS cutpoint of ≥1 percent seemed to identify a population whose survival with combined therapy was comparable to that of those treated at a CPS cutpoint of ≥10 percent [36],

although the correlation between TPS and CPS remains unknown. (See 'Squamous cell cancers' below.)

- **Is there temporospatial heterogeneity of PD-L1 expression within and between tumor sites, and is rebiopsy indicated?**

  Heterogeneity of PD-L1 expression within individual tumors and between tumor sites has been described for multiple cancer types. Within upper gastrointestinal tract tumors, PD-L1 expression displays marked spatial heterogeneity between baseline primary tumors and metastases (69 percent concordance in one study [40]) and temporal heterogeneity between tumors before and after chemotherapy (73 to 75 percent concordance in the same study). In comparisons between paired baseline primary and baseline metastatic tumors (spatial heterogeneity), only 42 percent of CPS 1+ primaries had corresponding CPS ≥1 metastases (the metastases for other patients were CPS <1). By contrast, 88 percent of individuals with CPS <1 primaries had CPS <1 metastases. Findings were similar for CPS at the cutpoint of ≥10. These data provide an argument against empiric use of ICIs in gastric cancer.

  The issue of temporal heterogeneity raises the question as to whether tumors should be rebiopsied. In this regard, 64 percent of tumors in this analysis that were PD-L1 CPS ≥1 at baseline stayed positive post-treatment, whereas 39 percent of PD-L1 CPS <1 tumors "became" CPS ≥1 posttreatment. But for CPS <10 at baseline, posttreatment biopsy was CPS ≥10 only 17 percent of the time. It is not uncommon in clinical practice to see initially PD-L1-negative tumors "become" PD-L1-positive after treatment. As a result, we tend to repeat biopsy when possible, especially if CPS is absent/low, but this is not yet a standard approach, and there is no strong evidence that this improves outcomes. A major caveat is that it is not known whether "chemo-induced" PD-L1 expression has the same biologic implication as "native" PD-L1 expression.

  Additional studies are needed to determine the optimal location and timing for measurement of these biomarkers, and this issue is under active study [41].

**HER2-negative adenocarcinoma** — For patients with gastric and GEJ adenocarcinoma, we suggest a chemotherapy backbone including both a fluoropyrimidine and oxaliplatin, rather than other chemotherapy combinations. Options include FOLFOX ( table 2) or CAPOX/XELOX ( table 3). (See 'Combination chemotherapy' below.)

Additional therapy is guided by tumor human epidermal growth factor receptor 2 (HER2) status and level of PD-L1 expression.

**CPS of 10 or more** — For patients with HER2-negative adenocarcinoma and CPS ≥10, we suggest the addition of either nivolumab or pembrolizumab to chemotherapy as this approach improved overall survival (OS) in randomized trials (CheckMate 649 [42-44] and KEYNOTE-859 [45]).

- **Nivolumab plus fluorouracil and oxaliplatin** – Nivolumab plus oxaliplatin-based chemotherapy is an option for patients with HER2-negative metastatic gastric or GEJ adenocarcinoma and CPS ≥5. The recommended nivolumab doses in combination with chemotherapy are:

  - 360 mg every three weeks in combination with every three-week chemotherapy (eg, capecitabine plus oxaliplatin)

  - 240 mg every two weeks in combination with every two-week chemotherapy (eg, FOLFOX)

  In an open-label phase III trial (CheckMate 649), 1581 patients with previously untreated HER2-negative, advanced/unresectable or metastatic gastric, GEJ, or esophageal adenocarcinoma were randomly assigned to either nivolumab (360 mg every three weeks or 240 mg every two weeks) plus chemotherapy or chemotherapy alone [42-44]. Chemotherapy regimens were oxaliplatin plus either leucovorin plus short-term infusional fluorouracil (FU; FOLFOX) or capecitabine (XELOX; also known as CAPOX). Although patients were enrolled regardless of PD-L1 expression, the CPS was ≥5 in 955 patients (60 percent). At median follow-up of approximately 36 months, compared with chemotherapy alone, nivolumab plus chemotherapy demonstrated the following results [44]:

  - **Entire study population** – Improved OS (median 13.7 versus 11.6 months; three-year OS 17 versus 10 percent, hazard ratio [HR] 0.79, 95% CI 0.71-0.88), improved progression-free survival (PFS; median 7.7 versus 6.9 months; three-year PFS 11 versus 7 percent, HR 0.79, 95% CI 0.71-0.89), and higher objective response rate (ORR; 58 versus 46 percent).

  - **CPS ≥5** – Improved OS (median 14.4 versus 11.1 months; three-year OS 21 versus

10 percent, HR 0.7, 95% CI 0.61-0.81), improved PFS (median 8.3 versus 6.1 months; three-year PFS 13 versus 8 percent, HR 0.7, 95% CI 0.6-0.81), and higher ORR (60 versus 45 percent).

- **Other CPS subgroups** – Similar OS for CPS <10 (median 12.4 versus 12.5 months, HR 0.91, 95% CI 0.79-1.06). Outcomes for other CPS subgroups are discussed separately. (See 'CPS of less than 5' below.)

- **Microsatellite instability (MSI-H) tumors** – For those with MSI-H tumors, outcomes are discussed separately. (See 'Mismatch repair deficient/MSI-H tumors' below.)

- **Toxicity** – More frequent grade ≥3 treatment-related adverse events (60 versus 45 percent), treatment discontinuation for toxicity (19 versus 10 percent) [44], and treatment-related deaths (17 versus 9 patients, 2 versus <1 percent) [42]. However, patients receiving nivolumab plus chemotherapy reported stable or improved health-related quality of life while on therapy and were at reduced risk of deterioration in health-related quality of life [46].

Based on the results of CheckMate 649, nivolumab was approved by the FDA, in combination with a fluoropyrimidine and platinum-containing regimen, for advanced or metastatic gastric and GEJ cancer and esophageal adenocarcinoma irrespective of PD-L1 expression [47]. However, in our view, the benefits of immunotherapy for adenocarcinomas with CPS <5 are not established. Notably, the European Medicines Agency (EMA) has restricted approval of nivolumab to those with PD-L1 CPS ≥5 [48]. Further details are discussed separately. (See 'CPS of less than 5' below.)

- **Pembrolizumab plus fluorouracil and platinum** – Pembrolizumab plus oxaliplatin-based chemotherapy is another initial treatment option for patients with HER2-negative metastatic gastric or GEJ adenocarcinoma and CPS ≥10 ( algorithm 1).

  In a double-blind, placebo-controlled phase III trial (KEYNOTE-859), the addition of pembrolizumab to chemotherapy improved OS and PFS [45]. In this study, 1579 patients with previously untreated HER2-negative, locally advanced, or metastatic gastric (79 percent) or GEJ (21 percent) adenocarcinoma were randomly assigned to the addition of either pembrolizumab (200 mg intravenously every three weeks for up to 35 cycles) or placebo to investigator's choice of fluoropyrimidine and platinum-

based chemotherapy (either FU plus cisplatin or CAPOX). At median follow-up of 31 months, relative to placebo plus chemotherapy, pembrolizumab plus chemotherapy demonstrated the following results:

- **Entire study population** – Improved OS (median 12.9 versus 11.5 months, HR 0.78, 95% CI 0.7-0.87) and PFS (median 6.9 versus 5.6 months, HR 0.76, 95% CI 0.67-0.85) and higher ORR (51 versus 42 percent).
- **CPS ≥1** – Improved OS (median 13 versus 11.4 months, HR 0.74, 95% CI 0.65-0.84) and PFS (median 6.9 versus 5.6 months, HR 0.72, 95% 0.63-0.82) and higher ORR (52 versus 43 percent).
- **CPS ≥10** – Improved OS (median 15.7 versus 11.8 months, HR 0.65, 95% CI 0.53-0.79) and PFS (median 8.1 versus 5.6 months, HR 0.62, 95% CI 0.51-0.76), and higher ORR (61 versus 43 percent).
- **Other CPS subgroups** – Outcomes for other CPS subgroups are discussed separately. (See 'CPS of 5 to less than 10' below and 'CPS of less than 5' below.)
- **MSI-H tumors** – For those with MSI-H tumors, outcomes are discussed separately. (See 'Mismatch repair deficient/MSI-H tumors' below.)
- **Toxicity** – Grade ≥3 toxicity rates for pembrolizumab plus chemotherapy versus placebo plus chemotherapy were 60 and 51 percent, respectively. Patients receiving pembrolizumab plus chemotherapy were more likely to have long-term immune-mediated endocrine toxicities, such as hypothyroidism. (See "Toxicities associated with immune checkpoint inhibitors", section on 'Autoimmune thyroid disease'.)

By contrast, in a separate phase III trial (KEYNOTE-062) of patients with HER2-negative gastric or GEJ adenocarcinoma, the addition of pembrolizumab to fluoropyrimidine and cisplatin-based chemotherapy failed to improve OS or PFS for those with CPS ≥1, OS for those with CPS between 1 and 9 [49], or OS for those with CPS ≥10 [50]. Unlike CheckMate-649 and KEYNOTE-859, patients in KEYNOTE-062 did not receive oxaliplatin-based chemotherapy. However, pembrolizumab plus chemotherapy and pembrolizumab monotherapy did benefit the subset of patients with both positive PD-L1 expression and dMMR/MSI-H. These data are discussed

separately. (See 'Mismatch repair deficient/MSI-H tumors' below.)

Based on the results of KEYNOTE-859, pembrolizumab, in combination with fluoropyrimidine- and platinum-based chemotherapy is approved by the FDA for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma [47]. However, for mismatch repair proficient (pMMR) gastric and GEJ adenocarcinoma, we restrict the use of pembrolizumab plus chemotherapy to patients with tumor CPS ≥10. This patient population derives an OS benefit from this combination whereas the absolute OS benefit is limited for those with pMMR adenocarcinoma and CPS <10. (See 'CPS of 5 to less than 10' below and 'CPS of less than 5' below.)

- **Is there a role for pembrolizumab monotherapy?** – We do not typically offer initial therapy with single-agent pembrolizumab outside of a clinical trial, including to patients whose tumors have CPS ≥10. In an exploratory analysis of a randomized trial (KEYNOTE-062), pembrolizumab alone prolonged OS relative to chemotherapy alone in patients whose tumors had a CPS ≥10, but this difference was not statistically tested. In addition, these and other data also suggest that patients who receive either immunotherapy alone (either as monotherapy or combination therapy [ie, nivolumab plus ipilimumab]) are at risk for worse PFS (ie, early disease progression or death) [43,50].

  In a phase III trial (KEYNOTE-062), 763 patients with previously untreated, advanced, gastric or GEJ adenocarcinoma with a CPS ≥1 (281 with a CPS ≥10) were randomly assigned to pembrolizumab alone, chemotherapy alone (cisplatin plus a fluoropyrimidine), or pembrolizumab plus chemotherapy [50]. At a median follow-up of approximately 29 months, data were as follows:

  - **CPS ≥1** – For patients with CPS ≥1, pembrolizumab monotherapy compared with chemotherapy demonstrated noninferior, but not superior, OS (median 10.6 versus 11.1 months, hazard ratio [HR] 0.91, 99% CI 0.69-1.18), worsened PFS (median 2 versus 6.4 months, HR 1.66, 95% CI 1.37-2.01) and lower objective response rate (15 versus 37 percent). Pembrolizumab had fewer any-grade (54 versus 92 percent) and grade 3 or 4 (17 versus 69 percent) adverse effects than chemotherapy.

  - **CPS ≥10** – In an exploratory analysis of patients with CPS ≥10, compared with

chemotherapy alone, pembrolizumab monotherapy prolonged OS, although this was not statistically tested (median 17.4 versus 10.8 months, HR 0.69, 95% CI 0.49-0.97) and demonstrated a non-statistically significant trend towards lower PFS (median 2.9 versus 6.1 months, HR 1.1, 95% CI 0.79-1.51).

**CPS of 5 to less than 10** — For patients with HER2-negative adenocarcinoma and CPS of 5 to less than 10, we suggest the addition of nivolumab to chemotherapy. In a phase III trial (CheckMate 649), for the subgroup with CPS ≥5, nivolumab plus chemotherapy improved OS versus chemotherapy alone [42-44]. (See 'CPS of 10 or more' above.)

We do not offer the combination of pembrolizumab plus chemotherapy to patients with a CPS of 5 to less than 10. Although this combination is approved by the FDA for the initial treatment of HER2-negative gastric or GEJ adenocarcinoma regardless of tumor CPS, data suggest limited absolute OS benefit for this combination in patients with CPS of 5 to less than 10. In our view, this limited OS benefit is outweighed by the increased toxicity and cost of this combination.

A phase III trial (KEYNOTE-859) demonstrated an OS benefit for adding pembrolizumab to fluoropyrimidine plus platinum-based chemotherapy among those with CPS ≥1, but it is unlikely that this OS benefit is meaningfully driven by those with a CPS of 5 to less than 10. In an exploratory subgroup analysis of KEYNOTE-859, among patients with CPS of 5 to less than 10, the addition of pembrolizumab to chemotherapy demonstrated a statistically significant improvement in OS (HR 0.83, 95% CI 0.7-0.98), but the absolute OS benefit is likely marginal (on the order of weeks at best). Further results of KEYNOTE-859 for the entire study population and other CPS subgroups are discussed separately. (See 'CPS of 10 or more' above and 'CPS of less than 5' below.)

**CPS of less than 5** — For patients with HER2-negative adenocarcinoma with CPS <5 and mismatch repair proficiency, we do not incorporate immunotherapy, given that the benefits are less clear in this population and may not outweigh the risks. Such patients are treated with chemotherapy alone.

Although clinical practice is variable and specific CPS cutpoints that define low PD-L1 expression vary between trials, data from randomized trials converge to generally demonstrate limited OS benefit for the addition of immunotherapy to chemotherapy in those with CPS <5. Data are as follows:

- **Nivolumab plus fluorouracil and oxaliplatin** – A phase III trial (CheckMate 649) evaluated the addition of nivolumab to fluorouracil and oxaliplatin-based chemotherapy in patients with previously untreated HER2-negative, advanced/unresectable or metastatic gastric, GEJ, or esophageal adenocarcinoma [42-44]. In an exploratory subgroup analysis, the addition of nivolumab to chemotherapy failed to improve OS in those with CPS <1 (median 13.1 versus 12.5 months, unstratified HR 0.95, 95% CI 0.74-1.24), CPS <5 (median 12.4 versus 12.3 months, unstratified HR 0.95, 95% CI 0.80-1.12), or CPS <10 (median 12.4 versus 12.5 months, HR 0.91, 95% CI 0.79-1.06) [43,44,49]. Interaction analysis of OS by PD-L1 CPS cutoffs was not provided. Further results of this study are discussed separately. (See 'CPS of 10 or more' above.)

  In another phase III trial (ATTRACTION-4) of patients from Asia with HER2-negative advanced or recurrent gastric or GEJ adenocarcinoma, the addition of nivolumab to chemotherapy (oxaliplatin plus either S-1 or capecitabine) improved PFS but failed to improve OS, regardless of TPS score [51]. Of note, TPS may not be as predictive as CPS for PD-L1 expression in upper gastrointestinal tract adenocarcinomas [27]. (See 'PD-L1 expression status in upper GI tract cancers' above.)

- **Pembrolizumab plus fluorouracil and platinum** – A phase III trial (KEYNOTE-859) evaluated the addition of pembrolizumab to FU and platinum-based chemotherapy in patients with previously untreated HER2-negative, locally advanced or metastatic gastric or GEJ adenocarcinoma [45]. In an exploratory subgroup analysis, the addition of pembrolizumab to chemotherapy failed to improve OS in those with CPS <1 (HR 0.92, 95% CI 0.73-1.17) and demonstrated limited OS benefit for those with CPS <10 (HR 0.86, 95% CI 0.75-0.98) [45]. Full results of this study are discussed separately. (See 'CPS of 10 or more' above.)

  Similarly, for another phase III trial (KEYNOTE-062), in an exploratory subgroup analysis of 318 patients with previously untreated HER2-negative gastric or GEJ adenocarcinoma, the addition of pembrolizumab to fluoropyrimidine and cisplatin-based chemotherapy failed to improve OS for those with CPS between 1 and 9 (median OS 12.5 versus 11 months, HR 0.84, 0.66-1.06) [49]. Of note, these patients did not receive oxaliplatin-based therapy.

  Another phase III trial (KEYNOTE-590) evaluated pembrolizumab plus

fluoropyrimidine and cisplatin-based chemotherapy in patients with esophageal SCC or gastric/GEJ adenocarcinoma [49,52,53]. In an exploratory subgroup analysis, the addition of pembrolizumab to chemotherapy failed to improve OS among the 100 patients with gastric/GEJ adenocarcinoma and CPS <10 (median OS 12.7 versus 8.4 months, HR 0.66, 95% 0.42-1.04) [49,52]. In extended follow-up, preliminary results from this trial continue to suggest no significant benefit for the addition of pembrolizumab to chemotherapy for subgroups with CPS <10, regardless of histology (HR 0.84, 95% CI 0.67-1.06), but a test for interaction was not provided [53]. Of note, these patients did not receive oxaliplatin-based therapy. Full results of this trial are discussed separately. (See 'Efficacy versus chemotherapy alone' below.)

### Squamous cell cancers

**Efficacy versus chemotherapy alone** — For patients with advanced SCCs and PD-L1 TPS ≥1 percent or CPS ≥10, we suggest first-line therapy with chemotherapy plus immunotherapy rather than chemotherapy alone.

For patients with SCC and PD-L1 TPS <1 percent or CPS <10, we also suggest chemotherapy plus immunotherapy rather than chemotherapy alone, given the generally greater activity of immune checkpoint inhibitors (ICIs) in SCC as compared with adenocarcinomas and meta-analysis data that suggest a significant survival benefit in this population, albeit of a lesser magnitude than for those with high PD-L1 expression [54]. However, for patients whose tumors express low or absent levels of PD-L1, we have a lower threshold to omit or discontinue immunotherapy in the presence of unfavorable baseline features (eg, CPS <1, significant non-cancerous lung disease, experiencing toxicity) than we would in a patient with PD-L1 high disease given the likely lesser degree of efficacy in this population.

We do not favor immunotherapy alone in tumors that have low PD-L1 expression due to concerns about early progression/death compared with chemotherapy alone [36,43,50,55]. Because of this concern, we restrict the use of immunotherapy alone (nivolumab plus ipilimumab) to patients with TPS ≥1 percent disease.

Support for upfront immunotherapy in esophageal SCCs is provided by the CheckMate 648 study (nivolumab plus FU and cisplatin, and nivolumab plus ipilimumab, an ICI that targets a different checkpoint, cytotoxic T-lymphocyte-associated protein 4 [CTLA4]), by the KEYNOTE-590 trial (pembrolizumab plus FU and cisplatin), by the ESCORT-1$^{st}$ trial

(camrelizumab plus paclitaxel and cisplatin), ORIENT-15 trial (sintilimab plus paclitaxel and cisplatin), and JUPITER-06 (toripalimab plus paclitaxel and cisplatin) trials.

- **CheckMate 648** – In the CheckMate 648 trial, 970 adults with previously untreated, advanced unresectable, recurrent, or metastatic esophageal SCC regardless of PD-L1 expression were randomly assigned to nivolumab (240 mg every two weeks) plus chemotherapy (fluorouracil [800 mg/m$^2$ daily, days 1 through 5] plus cisplatin [80 mg/m$^2$ on day 1] every four weeks), nivolumab (3 mg/kg every two weeks) plus ipilimumab (1 mg/kg every six weeks), or chemotherapy alone [36]. Overall 49 percent of the randomized patients had tumor cell PD-L1 ≥1 percent.

  Patients receiving nivolumab plus chemotherapy had a significantly longer median OS compared with chemotherapy alone in both the entire population (13.2 versus 10.7 months, HR 0.74, 95% CI 0.58-0.96) and in those with PD-L1 ≥1 percent according to the TPS (15.4 versus 9.1 months, HR 0.54, 95% CI 0.37-0.8). Patients receiving nivolumab plus ipilimumab also had a statistically significant OS benefit compared with chemotherapy alone in both the entire population (12.7 versus 10.7 months, HR 0.78, 95% CI 0.62-0.98) as well as in those with PD-L1 ≥1 percent (13.7 versus 9.1 months, HR 0.64, 95% CI 0.46-0.9). When the analysis was done according to CPS rather than TPS, among those with a CPS of 1 or more (824 of 906 patients), OS still favored nivolumab plus chemotherapy versus chemotherapy alone (median 13.8 versus 9.8 months). The best outcomes from combined therapy seemed to occur in those with either TPS ≥1 or CPS ≥10.

  Objective response rates were highest in the group receiving nivolumab plus chemotherapy, followed by nivolumab plus ipilimumab, and then chemotherapy alone (53, 35, and 20 percent, respectively).

  Among the subset of patients with tumor cell PD-L1 expression of <1 percent by TPS, the median OS was approximately 12 months in each treatment group (HR for the comparison of nivolumab plus chemotherapy versus chemotherapy alone 0.92), and no PFS benefit was apparent with the nivolumab plus chemotherapy regimens compared with chemotherapy alone. Among those with a CPS of <1, median OS was 9.9 months with nivolumab plus chemotherapy versus 12.1 months with chemotherapy alone.

  Rates of severe adverse effects were similar with ipilimumab/nivolumab and

chemotherapy alone (32 and 36 percent, respectively, with fewer than 20 percent of the patients in each group discontinuing therapy because of side effects), and slightly higher in the group receiving nivolumab plus chemotherapy (47 percent, with 34 percent resulting in treatment discontinuation), possibly because of the longer duration of therapy in this group (5.7 months, as compared with 2.8 and 3.4 months for the ipilimumab/nivolumab and chemotherapy alone, respectively).

The authors concluded that nivolumab plus chemotherapy or ipilimumab offered improved outcomes over chemotherapy alone in advanced previously untreated esophageal SCC. In our view, this trial demonstrated better overall and PFS as well as higher response rates and a longer duration of therapy with nivolumab plus chemotherapy versus nivolumab plus ipilimumab, and we generally favor nivolumab plus chemotherapy over nivolumab plus ipilimumab.

Largely based on these results, in May 2022, the FDA approved nivolumab, in combination with either platinum plus fluoropyrimidine-based chemotherapy or ipilimumab, for first-line treatment of patients with advanced or metastatic esophageal SCC, regardless of PD-L1 expression [56,57]. However, whether the addition of immunotherapy to chemotherapy benefits individuals with low PD-L1 expression is a controversial issue. Notably, the EMA restricts approval of nivolumab to esophageal SCCs with PD-L1 expression TPS ≥1 percent [54]. This issue is discussed in detail below. (See 'Low PD-L1 expression (squamous cell carcinoma)' below.)

- **KEYNOTE-590** – Additional support is provided by the phase III KEYNOTE-590 trial that randomly assigned 749 patients with previously untreated advanced/unresectable or metastatic esophageal adenocarcinoma, esophageal SCC, or GEJ Siewert type 1 adenocarcinoma regardless of PD-L1 expression to pembrolizumab (200 mg every three weeks for up to 35 cycles) plus chemotherapy (FU 800 mg/m$^2$ IV days 1 through 5 every three weeks for up to 35 cycles), and cisplatin (80 mg/m$^2$ IV every three weeks for up to 6 cycles), or the same schedule of chemotherapy alone [52]. The primary endpoints were OS and PFS. In an interim analysis at a median follow-up of 22.6 months, median survival was significantly better with combined therapy (12.4 versus 9.8 months, HR 0.73, 95% CI 0.62-0.86), as was median PFS (6.3 versus 5.8 months, HR 0.65, 95% CI 0.55-0.76). The confirmed objective response rate was higher with combined therapy (45 versus 29 percent),

with a median duration of response of 8.3 versus 6 months, and the incidence rates of grade 3 to 5 drug-related adverse events were 86 versus 83 percent.

There are two significant provisos to these data:

- When stratified according to PD-L1 expression, benefit was exclusively seen in the population with CPS ≥10 (median survival 13.5 versus 9.4 months in the pooled population of both adenocarcinoma and SCC; HR 0.62, 95% CI 0.49-0.78). There did not seem to be a benefit for adding pembrolizumab in those with CPS <10 (median survival 10.5 versus 10.6 months, HR 0.86, 95% CI 0.68-1.1).

- The results were driven more by SCC (median survival 13.9 versus 8.8 months, HR 0.57, 95% CI 0.43-0.75) than by adenocarcinomas (median OS 11.6 versus 9.9 months, HR 0.74, 95% CI 0.54-1.02), which formed a minority of the study population (27 percent). However, even among those with SCC the addition of pembrolizumab did not benefit those with CPS <10 (n = 247 patients, HR for OS 0.99, 95% CI 0.74-1.32).

In a later analysis of KEYNOTE-590 with median follow-up 34.8 months continued to show a significant survival benefit from the addition of pembrolizumab to chemotherapy in the combined population (median 12.4 versus 9.8 months, HR 0.73, 95% CI 0.63-0.86) and, in preplanned subgroups of those with PD-L1 CPS ≥10 (median 13.6 versus 9.4 months, HR 0.64, 95% CI 0.51-0.8), SCC (median 12.6 versus 9.8 months, HR 0.73, 95% CI 0.61-0.88), SCC and PD-L1 ≥10 (median 13.9 versus 8.8 months, HR 0.59, 95% CI 0.45-0.76) [53]. Unplanned subgroup analysis suggested no significant benefit for the addition of pembrolizumab to chemotherapy for any subgroup with CPS <10 (HR 0.84, 95% CI 0.67-1.06), but a test for interaction was not provided.

Nevertheless, largely based on the first analysis of KEYNOTE-590, the FDA approved pembrolizumab, in combination with platinum- and fluoropyrimidine-based chemotherapy, for the treatment of patients with metastatic or locally advanced esophageal or GEJ carcinoma (SCC and adenocarcinoma) with an epicenter 1 to 5 cm above the GEJ and who are not eligible for resection or chemoradiation, regardless of PD-L1 expression [58]. However, the benefit of adding immunotherapy to chemotherapy for tumors with low PD-L1 expression, especially adenocarcinomas, is controversial. Notably, the EMA has restricted approval of pembrolizumab to

esophageal cancers with CPS ≥10 [59].

The benefit of immunotherapy for adenocarcinomas with low PD-L1 expression is discussed above. (See 'CPS of less than 5' above.)

The benefit of immunotherapy for SCCs with low expression of PD-L1 is addressed in detail below. (See 'Low PD-L1 expression (squamous cell carcinoma)' below.)

**Low PD-L1 expression (squamous cell carcinoma)** — As noted above, largely based on the first analysis of KEYNOTE-590, the FDA approved pembrolizumab, in combination with platinum- and fluoropyrimidine-based chemotherapy, for the treatment of patients with metastatic or locally advanced esophageal or GEJ carcinoma (both SCC and adenocarcinoma) who are ineligible for resection or chemoradiation, and without regard for level of PD-L1 expression. However, data are mixed for the benefit of immunotherapy in patients with SCC and low PD-L1 expression.

Data for chemoimmunotherapy in patients with esophageal/gastric adenocarcinoma with low or absent PD-L1 expression is discussed above. (See 'CPS of less than 5' above.)

Data from clinical trials are mixed on the benefits of upfront immunotherapy in those with SCC and low PD-L1 expression.

- Several international trials (ie, not restricted to Asia) in patients with esophageal adenocarcinoma showed no OS benefit for the addition of immunotherapy to chemotherapy among those with low PD-L1 expression (ie, TPS <1 percent [CheckMate 648] or CPS <10 [KEYNOTE-590]) [36,52,60].

- By contrast, in another international clinical trial (RATIONALE-306) that used an alternative PD-L1 scoring system which resembles CPS (PD-L1 tumor area positivity [TAP]), the addition of immunotherapy (tislelizumab) to chemotherapy demonstrated a non-statistically significant trend towards improved OS among those with PD-L1 TAP <10 [61].

Several meta-analyses of randomized clinical trials suggest some benefit for immunotherapy in SCC with low PD-L1 expression. Data are as follows:

- One analysis of 17 randomized trials conducted in either the first- or second-line setting in either adenocarcinoma or SCC evaluated the OS benefit of

immunotherapy for high versus absent/low PD-L1 expression [62]. Among patients with SC, PD-L1 expression was the strongest predictor of benefit from immunotherapy (HR 0.6, 95% CI 0.53-0.68 for high TPS, and HR 0.84, 95% CI 0.75-0.95 for low TPS). Of the seven trials restricted to SCC, five trials enrolled Asian patients only. In addition, patients with SCC appeared to benefit more from ICIs than those with adenocarcinoma (HR 0.71, 95% CI, 0.67-0.77 for OS in SCC; HR 0.87, 95% CI, 0.8-0.96 for OS in adenocarcinoma). PD-L1 expression [ie, CPS ≥10 and TPS ≥1 percent]) also appeared to be more common in SCC than adenocarcinoma [62].

- A meta-analysis of five randomized trials [36,52,63-65] analyzed the benefit of adding immunotherapy to chemotherapy in patients with SCC stratified by PD-L1 expression (high versus low) using two expression scoring criteria (TPS ≥1/<1 percent, and CPS ≥10/<10) [66]. An OS benefit for chemoimmunotherapy relative to chemotherapy alone was seen in those with TPS <1 percent (HR 0.77, 95% CI 0.56-0.97) and CPS <10 percent (HR 0.77, 95% CI 0.66-0.89).

**Mismatch repair deficient/MSI-H tumors** — For patients with dMMR/MSI-H metastatic esophageal and gastric cancer (either SCC or adenocarcinomas), we recommend the addition of an ICI to chemotherapy, as this approach improves OS and can induce durable treatment responses. Immunotherapy alone (nivolumab plus ipilimumab or pembrolizumab monotherapy) is an acceptable alternative. Although data are lacking to guide the selection of therapy, we suggest FOLFOX plus nivolumab, followed by maintenance therapy for those patients without disease progression after three to four months of treatment. Options for maintenance therapy include nivolumab plus fluorouracil (FU); nivolumab monotherapy; or pembrolizumab monotherapy. In our clinical experience, this approach results in durable treatment responses and is well-tolerated.

For previously untreated patients with advanced or metastatic dMMR/MSI-H gastric and GEJ adenocarcinoma, studies suggest that the addition of an ICI to chemotherapy confers an OS benefit over chemotherapy alone. This approach is also extrapolated to those with MSI-H esophageal SCC, although such tumors are exceedingly rare and most dMMR/MSI-H gastric and esophageal tumors are adenocarcinoma on histology. Sensitivity to ICIs is generally seen with all dMMR/MSI-H cancer histologies, and the biological rationale for this is discussed separately. (See "Overview of advanced unresectable and metastatic solid tumors with DNA mismatch repair deficiency or high tumor mutational burden", section

on 'Biologic principles'.)

- Nivolumab **plus chemotherapy** – In a phase III trial (CheckMate 649), the addition of nivolumab to chemotherapy was evaluated in previously untreated advanced or metastatic gastric or GEJ adenocarcinoma [42-44]. In a subset analysis of 44 patients with dMMR/MSI-H tumors, the addition of nivolumab to chemotherapy improved OS (median 38 versus 12 months, HR 0.34, 95% CI 0.16-0.74) [44]. An OS benefit was also seen among the subset of 34 patients with both CPS ≥5 and dMMR/MSI-H tumors (median 45 versus 9 months, HR 0.29, 95% CI 0.12-0.71). The addition of nivolumab to chemotherapy increased grade ≥3 toxicity (60 versus 45 percent). Full results of CheckMate 649 are discussed separately. (See 'CPS of 10 or more' above.)

- Pembrolizumab **plus chemotherapy** – Studies in advanced dMMR/MSI-H gastric and GEJ adenocarcinoma suggest that the addition of pembrolizumab to chemotherapy improves OS [45,67]. As an example, in a phase III trial (KEYNOTE-859), the addition of pembrolizumab to chemotherapy was evaluated in previously untreated advanced or metastatic gastric or GEJ adenocarcinoma [45]. In a subset analysis of 39 patients with MSI-H tumors, the addition of pembrolizumab to chemotherapy improved OS (HR 0.34, 95% CI 0.18-0.66) and PFS (HR 0.27, 95% CI 0.14-0.53). The addition of pembrolizumab to chemotherapy increased grade ≥3 toxicity (60 versus 51 percent). Full results of KEYNOTE-859 are discussed separately. (See 'CPS of 10 or more' above.)

  An exploratory analysis of three separate trials evaluating pembrolizumab as initial (KEYNOTE-062) and later-line (KEYNOTE-059 and KEYNOTE-060) therapy for advanced or metastatic gastric or GEJ adenocarcinoma included a subgroup of 50 patients with tumors with dMMR/MSI-H and CPS ≥1. In this subgroup, relative to chemotherapy alone, pembrolizumab plus chemotherapy was associated with improved OS (median not reached versus 8.5 months), improved PFS (median not reached versus 6.6 months), and a higher ORR (65 versus 37 percent) [67]. Full results from this study are discussed separately. (See 'CPS of 10 or more' above.)

Immunotherapy alone is also an acceptable alternative, with equally good evidence for OS benefit and tolerability when compared with chemotherapy in randomized trials.

- **Nivolumab plus** ipilimumab – In a phase III trial (CheckMate 649), nivolumab plus ipilimumab was directly compared to chemotherapy alone in 813 patients with

previously untreated advanced or metastatic gastric or GEJ adenocarcinoma [43]. At minimum follow-up of 36 months, among the 22 patients with MSI-H tumors, nivolumab plus ipilimumab improved OS (median OS not reached versus 10 months, unstratified HR 0.28, 95% CI 0.08-0.92) with a higher ORR (70 versus 57 percent) relative to chemotherapy.

However, in the entire study population, nivolumab plus ipilimumab failed to improve OS over chemotherapy (median OS 12 months for both; HR 0.91, 95% CI 0.77 to 1.07) with worse PFS (median PFS 3 versus 7 months, HR 1.66, 95% CI 1.40-1.95) [43]. Nivolumab plus ipilimumab had less grade 3 to 4 toxicity than chemotherapy (38 and 46 percent).

- **Pembrolizumab** – An exploratory analysis of three separate trials evaluating pembrolizumab as initial (KEYNOTE-062) and later-line (KEYNOTE-059 and KEYNOTE-060) therapy for advanced or metastatic gastric or GEJ adenocarcinoma included a subgroup of 84 patients with dMMR/MSI-H tumors [67]. In this subgroup, relative to chemotherapy alone, pembrolizumab monotherapy was associated with improved OS (median not reached versus 9 months, one-year OS 79 versus 47 percent), improved PFS (median 11 versus 7 months), higher ORR (57 versus 37 percent), and longer duration of response (21 versus 7 months). Pembrolizumab had less grade 3 to 4 toxicity than chemotherapy (17 versus 69 percent). Full results from this study are discussed separately. (See 'CPS of 10 or more' above.)

The management of advanced dMMR/MSI-H gastric and esophageal tumors in second- and later-line therapy is discussed separately. (See "Second- and later-line systemic therapy for metastatic gastric and esophageal cancer", section on 'Defective mismatch repair'.)

**Selection of the chemotherapy backbone for combined therapy** — When immunotherapy is combined with chemotherapy in the first-line setting, the optimal chemotherapy backbone is not established. The CheckMate 649 and ATTRACTION-4 trials used an oxaliplatin-based regimen with nivolumab while the KEYNOTE-590 and KEYNOTE-062 trials used cisplatin and FU in conjunction with pembrolizumab. Regardless of the specific ICI, we generally prefer an oxaliplatin-containing regimen for most patients. (See 'Oxaliplatin combinations' below.)

Where camrelizumab is available (mainly China), a chemotherapy doublet of paclitaxel and

cisplatin, as was used in the ESCORT-1st trial, is an appropriate option. (See 'Squamous cell cancers' above.)

**HER2-positive adenocarcinomas**

**Assessing HER2 status** — Some patients with advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma have tumors that overexpress HER2. In GEJ adenocarcinoma, the heterogeneity of immunostaining for HER2 is greater than in other tumor types, such as breast cancer. Therefore, tumor-specific criteria have been developed to assess for HER2 expression in gastric and GEJ adenocarcinoma ( table 1 and algorithm 2).

These criteria incorporate the method of tissue sampling (biopsy versus surgical specimen) and immunohistochemistry (IHC) staining, with fluorescence in situ hybridization (FISH) for equivocal IHC results. High levels of HER2 expression are typically confirmed by either 3+ IHC staining or equivocal (2+ IHC staining) in conjunction with positive FISH. Further details on assessing HER2 status in gastric and GEJ adenocarcinoma are discussed separately. (See "Gastric cancer: Pathology and molecular pathogenesis", section on 'HER2 overexpression'.)

**Treatment approach** — For patients with HER2-positive adenocarcinomas ( algorithm 2), we suggest the addition of trastuzumab to chemotherapy. Preferred options include FOLFOX plus trastuzumab ( table 6) and CAPOX plus trastuzumab ( table 7). (See 'Trastuzumab plus chemotherapy' below.)

Additionally, for HER2-positive cancers that also have CPS ≥1, we suggest the addition of pembrolizumab to trastuzumab and chemotherapy. Preferred options include pembrolizumab plus FOLFOX and trastuzumab ( table 8) and pembrolizumab plus CAPOX and trastuzumab ( table 9). (See 'Pembrolizumab plus trastuzumab and chemotherapy' below.)

For patients who are ineligible for trastuzumab ( table 4), we offer an initial treatment approach similar to those with HER2-negative adenocarcinoma. (See 'Ineligible for trastuzumab' below.)

**Trastuzumab plus chemotherapy**

**Trastuzumab plus fluoropyrimidine and cisplatin** — In an open-label phase III

trial (ToGA), the addition of trastuzumab to fluoropyrimidine and cisplatin-based chemotherapy improved OS and PFS and was well-tolerated [68]. In this study, 594 patients with advanced HER2-positive gastric or GEJ adenocarcinoma were randomly assigned to six cycles of platinum-based chemotherapy (capecitabine plus cisplatin or infusional FU plus cisplatin) with or without trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every three weeks until disease progression or unacceptable toxicity).

At median follow-up of 17 to 19 months, the addition of trastuzumab to chemotherapy improved OS (median 14 versus 11 months, HR 0.74, 95% CI 0.6-0.91), PFS (median 6.7 versus 5.5 months, HR 0.71, 95% CI 0.59-0.86), and objective response rates (47 versus 35 percent). In an exploratory subgroup analysis, trastuzumab improved OS in the patients with HER2 IHC 3+ tumors (HR 0.66, 95% CI 0.5-0.87) but was less effective in those with IHC 2+ tumors (HR 0.78, 95% CI 0.55-1.1) and ineffective in those with HER2 gene-amplified (ie, FISH-positive) but non-protein-expressing (IHC 0 or 1+) tumors.

Grade 3 and 4 toxicities were similar between the two treatment arms (68 percent each), but the addition of trastuzumab to chemotherapy had higher rates of grade 3 or 4 diarrhea (9 versus 4 percent) and an asymptomatic decrease in left ventricular ejection fraction (5 versus 1 percent).

Based on the results of the ToGA trial, trastuzumab, in combination with cisplatin and a fluoropyrimidine, is approved by the FDA for the treatment of patients with metastatic HER2-positive gastric or GEJ adenocarcinomas who have not received prior treatment for metastatic disease [47].

**Trastuzumab plus fluoropyrimidine and oxaliplatin** — When selecting between chemotherapy regimens, we suggest adding trastuzumab to fluoropyrimidine plus oxaliplatin-based chemotherapy rather than fluoropyrimidine plus cisplatin-based chemotherapy as data suggest better OS and less toxicity with this approach.

In a meta-analysis of 155 prospective and retrospective cohort studies that included 557 patients with advanced HER2-positive gastric and GEJ adenocarcinoma, trastuzumab was evaluated in combination with various chemotherapy regimens for initial therapy [69]. Compared with trastuzumab, cisplatin, and a fluoropyrimidine (the regimen used in the ToGA trial), trastuzumab plus oxaliplatin and either capecitabine or FU was associated with improved OS (median 20.7 versus 16 months, HR 0.75, 95% CI 0.59-0.99) and less toxicity. Data from the ToGA trial are discussed separately. (See 'Trastuzumab plus

fluoropyrimidine and cisplatin' above.)

**Trastuzumab plus other chemotherapy agents** — Alternatively, trastuzumab may be combined with other regimens used for initial therapy in advanced gastric and GEJ adenocarcinoma (eg, FOLFIRI; paclitaxel with or without a platinum; fluorouracil [FU]; and docetaxel, cisplatin, and fluorouracil [DCF]). However, this is a less preferred approach as there are no randomized trials evaluating the addition of trastuzumab to these regimens.

In a meta-analysis of 15 prospective and retrospective cohort studies that included 557 patients with advanced HER2-positive gastric and GEJ adenocarcinoma, trastuzumab was evaluated in combination with various chemotherapy regimens for initial therapy [69]. Compared with trastuzumab, cisplatin, and a fluoropyrimidine (the regimen used in the ToGA trial), each chemotherapy regimen was associated with the following results:

- **Trastuzumab with a triplet chemotherapy (eg, docetaxel, a platinum, and a fluoropyrimidine) or with bevacizumab plus a doublet chemotherapy** – Similar OS and more toxicity.
- **Trastuzumab plus cisplatin and S-1** – Similar OS and with a different toxicity profile, including less hand-foot syndrome.
- **Trastuzumab plus cisplatin or capecitabine** – Worsened OS and more toxicity.

**Pembrolizumab plus trastuzumab and chemotherapy** — Based on data from phase I and II clinical trials [70,71], the combination of pembrolizumab, trastuzumab, and chemotherapy was evaluated in an international, double-blind, placebo-controlled phase III trial (KEYNOTE-811) [72,73]. In this study, 698 patients with HER2-positive advanced gastric or GEJ adenocarcinoma and no prior systemic therapy for advanced disease were randomly assigned to either pembrolizumab or placebo, in combination with trastuzumab and platinum plus fluoropyrimidine-based chemotherapy (investigator's choice of cisplatin plus FU or CAPOX) every three weeks for up to 35 cycles or until disease progression or unacceptable toxicity during this time period. Most patients had tumors with CPS ≥1 than CPS <1 (85 versus 15 percent).

At median follow-up of 38 months, in the entire study population, relative to the addition of placebo, the addition of pembrolizumab to trastuzumab plus chemotherapy demonstrated the following [72]:

- **Entire study population** – Improved PFS (median 10 versus 8 months, HR 0.73, 95% CI 0.61-0.87) and objective response rate (73 versus 60 percent). OS was also numerically higher, but the difference did not meet statistical significance (median 20 versus 17 months, HR 0.84, 0.7-1.01). Follow-up of OS is ongoing.

- **CPS ≥1** – Improved PFS (median 11 versus 7 months, HR 0.71, 95% CI 0.59-0.86), OS (median 20 versus 16 months, HR 0.81, 95% CI 0.67-0.98), and objective response rate (73 versus 58 percent). Results for those with CPS <1 are discussed separately. (See 'Regimens not used' below.)

Grade ≥3 toxicity rates were similar between the two treatment arms (58 versus 51 percent), and no new toxicity profiles were identified.

Pembrolizumab in combination with trastuzumab, fluoropyrimidine, and platinum-containing chemotherapy has accelerated approval from the FDA for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma whose tumors express PD-L1 (CPS ≥1) using an FDA-approved test [47]. (See "Principles of cancer immunotherapy", section on 'Diagnostic tests'.)

**Ineligible for trastuzumab** — For patients who are ineligible for trastuzumab (table 4), we offer an initial treatment approach similar to those with HER2-negative adenocarcinoma. Cardiac criteria that render a patient ineligible for adjuvant trastuzumab in breast cancer are available, and we extrapolate its use to advanced gastric and esophageal cancer to determine which patients are not candidates for trastuzumab.

We also do not offer initial therapy that integrates an alternative HER2-directed agent, such as lapatinib [74] or pertuzumab [75], due to lack of OS benefit for these agents in phase III trials.

**Regimens not used** — For patients with HER2-positive gastric and GEJ adenocarcinoma and CPS <1, we do not offer pembrolizumab in combination with trastuzumab and chemotherapy as data suggest no PFS benefit and a possible trend towards worsened OS [72].

A phase III trial (KEYNOTE-811) of treatment-naïve advanced HER2-positive gastric and GEJ adenocarcinoma included a subgroup of patients with CPS <1 [72]. Among this subgroup,

the addition of pembrolizumab demonstrated similar PFS (10 months each, HR 1.03, 95% CI 0.65-1.64) and objective response rates (69 percent each). At median follow-up of 28 months, OS was also numerically lower, but the difference did not meet statistical significance (16 versus 22 months, HR 1.61, 95% CI 0.98-2.64). Follow-up of OS is ongoing. Results for the entire study population in KEYNOTE-811 are discussed separately. (See 'Pembrolizumab plus trastuzumab and chemotherapy' above.)

For patients with HER2-positive gastric or GEJ adenocarcinoma, we also do not offer trastuzumab plus FOLFIRINOX. In a phase II trial, this combination demonstrated high objective response rates but with significant toxicity [76]. Further details of this regimen in HER2-negative adenocarcinoma are discussed separately. (See 'FOLFIRINOX' below.)

**Prognosis** — The association between HER2 expression/amplification and prognosis in gastric and GEJ adenocarcinoma is uncertain. Some studies suggest that HER2 is associated with improved survival while other have failed to demonstrate this association.

The following data are available:

- Retrospective evaluations of HER2 expression and gene amplification in relation to prognosis for gastric/GEJ adenocarcinomas have been performed in at least seven studies of prospectively enrolled clinical trial cohorts [77-83]. These studies adopted the HER2 interpretive criteria used in ToGA, and patients **did not** receive HER2-targeted therapy. The results are conflicting. Four studies found that HER2 was not associated with prognosis [78,79,81,83], while one reported a significant positive association [77,84], and one other reported a trend toward improved survival with HER2 overexpression [82]. In one study, HER2 overexpression was associated with shorter survival, but only among patients who received adjuvant postoperative chemoradiotherapy after potentially curative resection [80].

- While the prognostic impact of HER2 overexpression was not formally evaluated in the ToGA study, the median OS of patients in the control arm appeared to increase as HER2 protein expression levels increased (median survival durations were 7.2, 10.2, 10.8, and 12.3 months for those with IHC 0/FISH-positive, IHC 1+/FISH-positive, IHC 2+/FISH-positive, and IHC 3+/FISH-positive tumors, respectively) [68].

- By contrast, in a meta-analysis of 49 gastric cancer studies (n = 11,337, from 1990 to 2011, stage I to IV), patients with (versus without) HER2 overexpression had shorter

five-year OS (42 versus 52 percent) [85]. However, the generalizability of this meta-analysis (which did not include the seven studies or the ToGA trial results described above) may be limited because only one study was performed after disease-specific HER2 interpretive criteria were established through ToGA.

- Among patients with esophageal adenocarcinomas, the prognostic impact of HER2 has not been as extensively examined as it has been in gastric cancer (sample sizes typically <200 cases), but the data are likewise conflicting [86-91]. The largest study (n = 713), which used disease-specific HER2 interpretive criteria, found no association between HER2 overexpression and prognosis [86].

- In modern series, the prognostic impact of HER2 overexpression is likely to be linked to the use of anti-HER2 therapy. In one analysis of 924 patients with advanced esophagogastric cancer receiving first-line chemotherapy, those with HER2-positive tumors receiving HER2-targeted therapy had a significantly higher survival as compared with those with HER2-negative tumors (HR for death 0.75, 95% CI 0.61-0.91) [92].

**Chemotherapy options** — For SCC and adenocarcinomas that do not overexpress HER2 and are not candidates for immunotherapy, the choice of the chemotherapy regimen is empiric. For most patients who are candidates for aggressive combination therapy, we suggest a platinum- and fluoropyrimidine-containing doublet combination regimen. Acceptable options include FOLFOX, or XELOX/CAPOX.

Where S-1 is available, S-1 in combination with cisplatin is also a reasonable choice for first-line therapy that does not require central venous access.

For older patients or those with a poor performance status or significant comorbidity, we suggest monotherapy rather than combination chemotherapy. Options include leucovorin-modulated FU alone, single-agent capecitabine, single-agent irinotecan, or low-dose weekly taxanes.

**Single-agent chemotherapy** — In general, combination chemotherapy regimens provide higher response rates than do single agents, but this translates into only modestly longer durations of disease control and survival, which are measured in weeks to a few months. Single-agent chemotherapy is an appropriate option for patients who are not candidates for aggressive combination chemotherapy. Another option for frail or

older adult individuals is reduced-dose XELOX/CAPOX. (See 'Chemotherapy dosing in older and frail patients' below.)

- **Taxanes and irinotecan** – In general, response rates with taxane or irinotecan monotherapy are slightly higher than those seen with older agents, such as methotrexate and doxorubicin, but toxicity is prominent in many cases, and median survival durations have not been consistently greater than nine months with any agent. As examples:

  - In multiple studies, monotherapy with either single-agent paclitaxel or docetaxel produced response rates in the range of 15 to 24 percent [8-10,93-97].

  - In two reports involving 83 previously untreated patients, irinotecan was associated with response rates of 14 and 20 percent, respectively [98,99].

- **Fluoropyrimidines** – Efficacy is modest for leucovorin-modulated FU [100-102].

  Several orally active fluoropyrimidines are available, which, as single agents, are associated with response rates as high as 41 percent, but median survival durations have not exceeded nine months in any report [103-110]. Phase III studies have demonstrated equivalence between infusional FU, capecitabine, and S-1.

  Patients who are receiving a capecitabine-containing regimen should probably not take proton pump inhibitors concurrently. Concerns have been raised that higher gastric pH levels may inhibit dissolution and absorption of capecitabine, adversely impacting efficacy [111,112].

  S-1 is an oral formulation of the following components in a 1:0.4:1 ratio [105]: ftorafur (tegafur), the prodrug for FU; gimeracil (5-chloro-2,4-dihydroxypyridine), an inhibitor of dihydropyrimidine dehydrogenase (DPD), which prevents its degradation in the gastrointestinal tract, thus prolonging its half-life [106]; and oteracil (potassium oxonate), a specific inhibitor of one of the enzymes (orotate phosphoribosyl transferase) that phosphorylates FU in the intestine. Phosphorylated FU is thought to be mainly responsible for treatment-related diarrhea.

  The efficacy of S-1 alone (40 mg/m$^2$ orally twice a day on days 1 to 28 every six weeks) was shown in the phase III JCOG 9912 trial, which was powered to demonstrate noninferiority of S-1 alone and superiority of irinotecan plus cisplatin

over infusional FU monotherapy in 704 patients with unresectable or recurrent, previously untreated gastric adenocarcinoma [107].In the primary endpoint, PFS, S-1 was not inferior to infusional FU, and there were trends suggesting superiority over infusional FU (median PFS 4.2 versus 2.9 months). The response rate was higher with S-1 than with FU (28 versus 9 percent), and median OS was 11.4 versus 12.3 months. S-1 was associated with more grade 3 or 4 diarrhea than FU (8 versus <1 percent). Otherwise, the side effect profile was comparable.

S-1 monotherapy (40 to 60 mg twice daily on days 1 to 28 every six weeks) was directly compared with single-agent capecitabine (1250 mg/m$^2$ twice daily on days 1 to 14 every 21 days) in a Korean randomized phase II trial involving 91 older patients with previously untreated, advanced gastric cancer [108]. The two regimens were comparable with respect to overall response rate (29 versus 20 percent for S-1 and capecitabine, respectively), median time to tumor progression (4.2 versus 4.7 months), OS (median 8.2 versus 9.5 months), and treatment-related toxicity, with the exception of hand-foot syndrome (0 versus 7 percent).

Thus, S-1 monotherapy appears active and well tolerated in cisplatin- and paclitaxel-refractory disease [109], and where available (not yet in the United States), it is a reasonable option in this setting; however, efficacy is more modest in patients with a poor performance status [110]. At least in Asian populations, S-1 monotherapy appears to be inferior to combination chemotherapy containing S-1 in previously untreated patients with advanced esophagogastric cancer [113,114]. (See 'Cisplatin plus a fluoropyrimidine' below.)

**Combination chemotherapy** — Higher response rates (up to 65 percent) are reported in phase II trials evaluating combination therapy in patients with advanced esophageal and gastric cancer. However, almost without exception, response rates have been lower in the setting of randomized trials. Furthermore, whether the higher response rates seen with combination as compared with single-agent chemotherapy translate into longer response duration or survival remains uncertain. In general, the higher response rates seen with combination regimens has translated into only modestly longer durations of disease control and survival, which are measured in weeks to a few months [17,18].

**Oxaliplatin combinations** — Although oxaliplatin combinations have been most extensively studied for metastatic colorectal cancer, they are also active in the treatment

of esophagogastric cancer. A variety of different regimens have been studied in phase II trials (FOLFOX; epirubicin, oxaliplatin, and infusional FU [EOF]; XELOX/CAPOX; S-1 plus oxaliplatin; docetaxel plus oxaliplatin with or without FU or capecitabine), all of which are associated with response rates in the range of 40 to 67 percent and median survival durations between 8 and 15 months [115-129]. (See "Treatment protocols for esophagogastric cancer".)

Regimens containing oxaliplatin and a taxane are discussed below. (See 'Docetaxel-containing' below.)

At least five phase III trials have directly compared oxaliplatin-based regimens with cisplatin-containing regimens (including epirubicin, cisplatin, and infusional FU [ECF]), all of which suggest at least comparable efficacy when oxaliplatin is substituted for cisplatin in combination regimens for patients with advanced esophagogastric cancer [115,130-133]. A meta-analysis of the REAL-2 trial [130] plus two other randomized phase II trials [115,134] that compared oxaliplatin-based regimens with cisplatin-based regimens showed that oxaliplatin was associated with significant improvements in PFS (HR 0.88, 95% CI 0.8-0.98) and OS (HR for death 0.88, 95% CI 0.78-0.99), and with less neutropenia, anemia, alopecia, and thromboembolic events, but with more neurotoxicity and diarrhea [135].

Benefit for the FOLFOX regimen is also supported by the results of CALGB 80403, a randomized phase II trial comparing ECF with FOLFOX ( table 2), both in combination with cetuximab, which concluded that response rates, PFS, and median OS were similar with either regimen [128,129].

**FOLFIRINOX** — We do not suggest oxaliplatin plus irinotecan, leucovorin, and FU (FOLFIRINOX) as a preferred option for first-line therapy, either in the setting of HER2-negative or HER2-positive disease.

Emerging data suggest high response rates with first-line oxaliplatin and irinotecan-containing regimens such as FOLFIRINOX, albeit with greater toxicity than is typically seen for regimens containing either oxaliplatin or irinotecan. As an example, a phase II open-label study administered the FOLFIRINOX regimen ( table 10) to 67 patients with previously untreated metastatic gastroesophageal cancer; the 26 who had HER2-positive disease received concurrent trastuzumab [76]. The objective response rate in those with HER2-negative disease was 61 percent, median PFS was 8.4 months, and median OS was

15.5 months. The most common severe toxic effects were neutropenia (91 percent, 79 percent grade ≥3), diarrhea (63 percent, 13 percent grade ≥3), peripheral sensory neuropathy (61 percent, 3 percent grade ≥3), nausea (48 percent, 6 percent grade ≥3), and fatigue (45 percent, 6 percent grade ≥3). The data for patients with HER2-positive disease are addressed separately. (See 'Regimens not used' above.)

**Cisplatin plus a fluoropyrimidine**

- **Cisplatin plus FU** – The combination of cisplatin plus FU has been one of the most commonly used regimens in both metastatic and localized esophageal cancer due to its activity and well-established toxicity profile. In a randomized phase II study, 88 patients with locally advanced or metastatic esophageal SCC were assigned to either single-agent cisplatin (100 mg/m$^2$ every 21 days) or the same dose of cisplatin combined with FU (1000 mg/m$^2$ per day by continuous infusion on days 1 to 5) [136]. Although the response rate was higher for the doublet (35 versus 19 percent), the median survival (33 versus 28 weeks) and one-year survival rate (34 versus 27 percent) were not significantly different. Furthermore, there was a 17 percent treatment-related mortality rate (primarily due to sepsis and cerebrovascular episodes) in the cisplatin plus FU arm.

  A similar degree of activity (response rate 27 percent; median survival six months) was reported with much less toxicity (treatment-related mortality rate 3 percent) in a second study that used split-dose cisplatin (20 mg/m$^2$ per day on days 1 to 5) in combination with leucovorin calcium and bolus FU (300 mg/m$^2$ per day for five days) [137].

  Combinations of cisplatin plus FU and an anthracycline are discussed below. (See 'Epirubicin, cisplatin, and fluorouracil' below.)

- **Cisplatin plus capecitabine** – Capecitabine is a unique, rationally designed oral fluoropyrimidine that undergoes a three-step enzymatic activation process, the last of which occurs selectively within the tumor tissue itself. The drug passes intact through the bowel and reaches the liver, where it is converted first into deoxyfluorocytidine by a carboxylesterase and then into 5-deoxfluorouridine, which reaches the tumor, where it is transformed into its active form, FU, by thymidine phosphorylase.

The comparable efficacy of regimens substituting capecitabine for infusional FU was directly studied in two randomized trials [130,138].

A meta-analysis of these two trials concluded that, compared with FU combinations, capecitabine combinations were associated with higher response rates (odds ratio 1.38, 95% CI 1.1-1.73) and better OS (HR for death 0.87, 95% CI 0.77-0.98) [139].

Although these data suggest that the efficacy of regimens that substitute capecitabine for infusional FU is at least as good and that the use of capecitabine allows patients to avoid infusion pumps and a central venous catheter, the out-of-pocket cost of capecitabine is significantly higher than FU. This may be an important issue for patients whose health insurance coverage requires significant out-of-pocket expense for the capecitabine. Additionally, an oral chemotherapy agent requires both patient motivation and reliable upper gastrointestinal tract function.

- **Cisplatin plus S-1** – S-1 is an oral fluoropyrimidine that includes ftorafur (tegafur), gimeracil (5-chloro-2,4-dihydroxypyridine, a potent inhibitor of DPD), and oteracil (potassium oxonate, which inhibits phosphorylation of intestinal FU, thought responsible for treatment-related diarrhea). (See 'Single-agent chemotherapy' above.)

  S-1 in combination with cisplatin is highly active in Asian patients [113,140]. A report from the SPIRITS trial supports a significant benefit for combined S-1 plus cisplatin over S-1 alone in terms of both response rate (54 versus 31 percent) and median survival (13 versus 11 months, p = 0.04) in an Asian population [113]. Rates of grade 3 or 4 neutropenia (40 versus 11 percent), anemia (26 versus 4 percent), nausea (11 versus 1 percent), and anorexia (30 versus 6 percent) were also significantly higher.

  A subsequent randomized phase II trial from Japan demonstrated comparable outcomes for cisplatin plus S-1 compared with cisplatin plus capecitabine for first-line treatment of advanced gastric cancer [141].

  Ftorafur is metabolized differently in Western and Asian populations on account of polymorphic differences in the cytochrome P450 2A6 (*CYP2A6*) gene; as a result, the maximally tolerated dose differs. Western experience with combined S-1 plus cisplatin for advanced gastric cancer is limited but also promising [142,143]. As an example, in a multicenter phase II trial in which 72 patients received S-1 (25 mg/m$^2$

twice daily on days 1 through 21) plus cisplatin (75 mg/m$^2$ on day 1) every 28 days, the objective response rate was 55 percent, and the median duration of response was more than five months [143]. The safety profile was favorable; the most frequent grade 3 or 4 toxicities were fatigue/asthenia (24 percent), emesis (17 percent), nausea (15 percent), diarrhea (13 percent), and neutropenia (19 percent).

The results from the phase II S-1 plus cisplatin trial led to the initiation of a global prospective randomized phase III trial, the FLAGS trial, which randomly assigned 1053 patients to cisplatin plus either FU or S-1. Median OS (the primary endpoint) was not significantly inferior with cisplatin plus S-1 as compared with cisplatin plus FU (8.6 versus 7.9 months) [144]. Furthermore, cisplatin plus S-1 had a more favorable side effect profile than cisplatin plus FU (grade 3 or 4 neutropenia in 19 versus 40 percent, stomatitis in 1 versus 14 percent, and hypokalemia in 4 versus 11 percent) and fewer treatment-related deaths (2.5 versus 4.9 percent) [145]. The lower cisplatin dose intensity in the cisplatin plus S-1 arm (75 versus 100 mg/m$^2$ on day 1 with cisplatin plus FU) may have contributed to the survival and toxicity results.

This study was not seen as a success, as many expected superiority of cisplatin plus S-1 over cisplatin plus FU based on the JCOG 9912 study (described above) [107]. Although a subgroup analysis suggested a possible survival benefit for cisplatin plus S-1 in the subset of patients with diffuse gastric cancer, there was a lack of superiority for cisplatin plus S-1 over cisplatin plus FU in a later randomized trial that focused specifically on diffuse gastric cancer [146].

**Irinotecan-containing regimens** — Several trials have assessed the benefit of irinotecan combined with docetaxel, cisplatin, fluoropyrimidines, or combinations of these drugs, but no superiority has been shown in phase III trials for any irinotecan-based regimen over a cisplatin-based triplet combination. Thus, irinotecan-based combinations cannot be considered to be preferable to a platinum-containing regimen for first-line therapy.

Irinotecan has been combined with fluoropyrimidines, cisplatin, and docetaxel. In the previously described meta-analysis, the comparison of irinotecan-containing versus non-irinotecan-containing regimens (mainly FU/cisplatin) revealed a nonstatistically significant trend toward better survival with irinotecan (HR for death 0.86, 95% CI 0.73-1.02) [147].

- **Irinotecan plus fluoropyrimidines or cisplatin** – The superiority of FOLFIRI (

table 11) over FU plus leucovorin with or without cisplatin was shown in a French randomized phase II trial involving 136 patients with advanced gastric cancer [148]. Compared with FU plus leucovorin alone or with cisplatin, the group receiving FOLFIRI had significantly higher response rates (40 versus 13 and 27 percent, respectively) and significantly longer median PFS (6.9 versus 3.2 and 4.9 months, respectively) and OS (11.3 versus 6.8 and 9.5 months, respectively). Roughly similar outcomes (response rates 42 to 44 percent, median survival 10 to 12 months) have been obtained using irinotecan in combination with oral capecitabine [149-151] and using irinotecan plus S-1 [152].

Irinotecan plus cisplatin is also active and well tolerated, particularly when administered weekly [107,153-157]. The superiority of cisplatin (80 mg/m$^2$ on day 1 every 28 days) plus irinotecan (70 mg/m$^2$ on days 1 and 15) as compared with infusional FU alone was shown in the phase III JCOG 9912 trial (described above) [107]. The response rate (38 versus 9 percent) and PFS (4.8 versus 2.9 months) were both significantly higher with cisplatin plus irinotecan. However, rates of grade 3 or 4 toxicity were also significantly higher (neutropenia [65 versus 1 percent], hyponatremia [23 versus 6 percent], anorexia [33 versus 13 percent], diarrhea [9 versus <1 percent], and nausea [21 versus 7 percent]).

Modest superiority of FOLFIRI over epirubicin plus cisplatin and capecitabine (ECX) was suggested in a French intergroup trial that randomly assigned 416 patients with previously untreated, advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma to FOLFIRI or ECX [158]. While there was a slight advantage in terms of time to treatment failure that favored FOLFIRI (5.1 versus 4.2 months), there were no significant differences in median PFS, OS, or response rates. Furthermore, while FOLFIRI was better tolerated overall (rate of grade 3 or 4 toxicity 69 versus 84 percent with ECX), the difference was only in hematologic adverse events (38 versus 65 percent); the rate of grade 3 or 4 nonhematologic adverse events was nearly identical (53 versus 54 percent).

**Triplet regimens** — We do not prefer triplet regimens over doublet regimens in patients receiving chemotherapy alone. In our view, these regimens are more toxic than a fluoropyrimidine plus platinum doublet, and they have not been shown to improve OS. (See 'Is there an optimal combination regimen?' below.)

**Epirubicin, cisplatin, and fluorouracil** — ECF ( table 12) was associated with a response rate of 71 percent in a report involving 128 patients with advanced disease [159]. In a subsequent randomized trial, 274 patients with advanced esophagogastric adenocarcinoma or undifferentiated cancer were randomly assigned to ECF or FU, doxorubicin, and methotrexate (FAMTX) [5]. ECF was associated with a superior response rate (45 versus 21 percent) and median survival (8.9 versus 5.7 months). ECF caused more alopecia and nausea, while FAMTX was associated with more hematologic toxicity and infections. (See "Treatment protocols for esophagogastric cancer".)

Newer regimens that combine short-term, high-dose infusional FU with leucovorin modulation (eg, FOLFOX), or capecitabine plus cisplatin may be more effective than older regimens in which cisplatin was combined with bolus FU alone [115,160-162]. This has led to questions as to the contribution of the anthracycline to the efficacy of ECF:

- A report of the CALGB 80403 (Alliance) trial, a randomized phase II trial in which cetuximab was added to ECF, irinotecan plus cisplatin, or FOLFOX, concluded that response rates, PFS, and median OS were comparable in the ECF and FOLFOX groups [128]. However, this trial included cetuximab in both arms, and it was neither designed nor intended as a noninferiority trial of FOLFOX versus ECF.

- An individual patient data meta-analysis of the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration group concluded that there was no role for epirubicin in combination with a fluoropyrimidine and a platinum agent [163].

Thus, the contribution of the anthracycline and the benefit of ECF over other modern fluoropyrimidine-containing regimens (eg, FOLFOX, XELOX/CAPOX) remain unanswered questions.

- **The REAL trial** – The REAL trial was a landmark large randomized trial reported in 2008 that compared four different chemotherapy regimens in 1002 patients with advanced gastric cancer: ECF, ECX ( table 13), EOF, and EOX ( table 14) [130]. The study was sufficiently powered to demonstrate noninferiority. (See "Treatment protocols for esophagogastric cancer".)

  As noted above, this trial (and a second one) showed that outcomes were comparable when capecitabine was substituted for infusional FU in the ECF regimen, a finding that was reinforced in a subsequent meta-analysis of both trials. (See

'Cisplatin plus a fluoropyrimidine' above.)

They also showed, as did the meta-analysis [147], that outcomes were comparable when oxaliplatin was substituted for cisplatin in the ECF regimen. (See 'Oxaliplatin combinations' above.)

**Docetaxel-containing** — Most (but not all [164]) docetaxel combinations with cisplatin, FU, capecitabine, or irinotecan are active in advanced gastric and gastroesophageal adenocarcinoma and esophageal SCC, but more toxic than doublet regimens [165-179].

- **Docetaxel, cisplatin, and FU (DCF) and modified DCF** – The DCF (or TCF) regimen ( table 15) was compared with cisplatin plus FU alone in the multinational TAX-325 trial, which enrolled 457 patients with chemotherapy-naïve advanced gastric cancer [165]. The group receiving docetaxel did significantly better in terms of response rate (37 versus 25 percent), time to tumor progression (5.6 versus 3.7 months), and two-year survival (18 versus 9 percent). The incidence of grade 3 or 4 diarrhea (20 versus 8 percent) and neutropenia (30 versus 14 percent) was higher with triplet therapy.

  Based on these results, docetaxel was approved in the United States and Europe, in combination with cisplatin and FU, for the treatment of advanced gastric cancer. However, the contribution of cisplatin remains uncertain. Similar results (overall response rate 38 percent, median survival 9.5 months) are reported using docetaxel and infusional FU without cisplatin [168].

  A modified schedule of DCF is associated with preserved efficacy and improved tolerability ( table 16) [180]. In a randomized comparison of modified DCF (without prophylactic growth factor support) versus standard DCF (with growth factor support) in 85 patients with previously untreated, metastatic gastric adenocarcinoma, modified DCF was more efficacious (median OS 18.8 versus 12.6 months) and, even without growth factor support, less toxic [181]. (See "Treatment protocols for esophagogastric cancer".)

- **Docetaxel, oxaliplatin, and FU** – Docetaxel, oxaliplatin, infusional FU, and leucovorin (FLOT) is a commonly used regimen in the neoadjuvant setting for gastric cancer. (See "Adjuvant and neoadjuvant treatment of gastric cancer", section on

'FLOT'.)

At least two trials have explored the benefit of taxane-, fluoropyrimidine-, and oxaliplatin-containing triplet therapy compared with an oxaliplatin-containing doublet, and they have come to opposite conclusions:

- In one trial, 143 patients aged 65 or older with locally advanced or metastatic esophagogastric cancer were randomly assigned to FOLFOX with or without docetaxel 50 mg/m$^2$ every two weeks [127]. There was a trend toward longer PFS with triplet therapy, but there was no difference in OS. Furthermore, triplet therapy was also associated with significantly worse toxicity.

- In the second randomized phase II trial, 248 patients with locally recurrent or metastatic gastric adenocarcinoma were randomly assigned to docetaxel plus oxaliplatin; docetaxel, oxaliplatin, and FU (TEF); or docetaxel, oxaliplatin, and capecitabine (TEX) [126]. The TEF combination proved superior for objective response rate (46 versus 26 and 23 percent for TEX and docetaxel plus oxaliplatin, respectively) and median PFS (7.66 versus 5.55 and 4.5 months, respectively). The frequency and type of adverse events were similar across all three groups.

**Is there an optimal combination regimen?** — As noted above, there is no globally accepted first-line chemotherapy regimen for advanced, HER2-negative esophagogastric cancer, and practice is variable [182]. Although multiple trials have been conducted of different chemotherapy regimens for first-line therapy, direct comparisons (head-to-head phase III randomized trials) of many regimens are lacking. When multiple specific interventions are compared across trials, a network of studies can be established where all the studied interventions are linked to each other by individual trials. Network meta-analysis (also termed "mixed treatment comparison" or "multiple treatment comparison") evaluates all studies and all interventions simultaneously to produce multiple pairwise estimates of the relative effects of each intervention compared with every other intervention, allowing both direct and indirect comparisons to be made.

A network meta-analysis of first-line chemotherapy for advanced esophagogastric cancer that incorporated 17 different chemotherapy regimens with 37 direct comparisons for OS (50 trials, 10,249 patients) and PFS (34 trials, 7795 patients) came to the following conclusions combining direct and indirect effects [17]:

- All treatments resulted in better OS and PFS as compared with best supportive care alone, except for anthracycline monotherapy. Fluoropyrimidine- and non-cisplatin-containing doublets, fluoropyrimidine-cisplatin doublets, and all triplet regimens showed significant gains in OS compared with a fluoropyrimidine alone.

- A fluoropyrimidine doublet containing oxaliplatin or irinotecan significantly improved OS compared with a fluoropyrimidine plus cisplatin (for a fluoropyrimidine plus irinotecan, the HR for death was 0.85, 95% CI 0.71-0.99; for a fluoropyrimidine plus oxaliplatin, the HR was 0.83, 95% CI 0.71-0.98). The cisplatin-fluoropyrimidine doublet was also associated with more grade 3 or 4 toxicity.

- Anthracycline-containing triplets (eg, ECF, EOX) and the docetaxel-containing triplet DCF showed no benefit over fluoropyrimidine doublets in either OS or PFS, and they were more toxic.

- A triplet regimen containing a fluoropyrimidine, oxaliplatin, and a taxane (eg, TEX, TEF) significantly improved PFS (but not OS) when compared with a fluoropyrimidine doublet with a taxane (HR for progression 0.61, 95% CI 0.38-0.99), a fluoropyrimidine plus irinotecan (HR 0.62, 95% CI 0.38-0.99), and a fluoropyrimidine plus oxaliplatin (HR 0.67, 95% CI 0.44-0.99). Furthermore, the triplet regimen was more toxic than a fluoropyrimidine plus oxaliplatin.

- Overall, based on efficacy and toxicity, fluoropyrimidine doublets (a fluoropyrimidine plus oxaliplatin, a fluoropyrimidine plus a taxane, or a fluoropyrimidine plus irinotecan) were preferred as first-line therapy over cisplatin doublets, anthracycline triplets, and DCF.

**Chemotherapy dosing in older and frail patients** — At least with the CAPOX regimen, dose attenuation does not compromise outcomes and that starting treatment with lower initial doses in frail/older individuals is a reasonable strategy. Whether this general principle of dose-attenuated therapy applies to other chemotherapy regimens are both not clear.

Most trials of palliative chemotherapy have not included frail or older patients, and the benefits and risks of chemotherapy in these patients are less certain. At least some data suggest that lower initial chemotherapy doses provide noninferior cancer control and better tolerability in this setting.

Optimal chemotherapy dosing for the XELOX/CAPOX regimen was addressed in a trial in which 514 older/frail patients with advanced esophagogastric cancer, including SCC histology, with an adequate baseline comprehensive geriatric assessment, a glomerular filtration rate (GFR) ≥30 mL/min and a total bilirubin <2 times the upper limit of normal (ULN) were randomly assigned to standard 21-day cycles of oxaliplatin (130 mg/m$^2$ on day 1) plus capecitabine (625 mg/m$^2$ twice daily on days 1 to 21), the same regimen with 80 percent of the usual doses, or the same regimen with 60 percent of the usual doses [183]. All patients with a GFR of 30 to 50 mL/min or a total bilirubin of 1.5 to 2 times the ULN received 75 percent of the allocated capecitabine doses. Noninferiority of the lower-dose regimens was assessed primarily using PFS at 12 months, with a noninferiority boundary of 1.34. Patient experience during chemotherapy was assessed using overall treatment utility (OTU), a composite outcome based on clinician-assessed clinical benefit and patient-assessed tolerability, quality of life, and perceived satisfaction with treatment. A good OTU required clinical benefit as scored by the clinician plus patient satisfaction with treatment, no major toxicity, and no decline in quality of life. By contrast, a poor OTU required both a clinician score of "no benefit" and patient dissatisfaction with treatment, major toxicity or deterioration in quality of life, or patient death during treatment.

Overall, the lowest doses tested provided noninferior cancer control and the best patient experience (as assessed by the OTU, toxicity, and quality of life). Compared with standard doses, noninferiority was confirmed for both the 80 percent dose regimen (HR for PFS 1.09, 95% CI 0.89-1.32) and the 60 percent dose regimen (HR 1.1, 95% CI 0.9-1.33). Median OS was comparable in all three groups (7.5, 6.7, and 7.6 months, respectively). No subgroup (age, performance status, extent of frailty, baseline geriatric assessment) clearly benefited from higher-dose therapy. The study did not address whether clinicians should subsequently attempt dose escalation if initial doses of XELOX/CAPOX are tolerated.

## INVESTIGATIONAL AGENTS

**Zolbetuximab** — Zolbetuximab is an investigational monoclonal antibody that targets CLDN18.2, which is expressed by gastric and gastroesophageal junction (GEJ) cancer [184]. In separate randomized placebo-controlled phase III trials (SPOTLIGHT and GLOW), the addition of zolbetuximab to oxaliplatin-based chemotherapy (either FOLFOX or CAPOX) improved progression-free survival (PFS) and overall survival (OS) in patients with previously untreated locally advanced or unresectable, human epidermal growth factor

receptor 2-negative, CLDN18.2-positive gastric or GEJ adenocarcinoma [185,186].

**Other agents**

- **Adenocarcinoma** – In patients with previously untreated advanced gastric or GEJ adenocarcinoma, other immunotherapy agents that have demonstrated an OS benefit when combined with chemotherapy in randomized trials include sintilimab (ORIENT-16) [187] and tislelizumab (RATIONALE-305) [188].

- **Squamous cell carcinoma (SCC)** – In patients with previously untreated advanced esophageal SCC, other immunotherapy agents that have demonstrated an OS benefit when combined with chemotherapy (cisplatin or oxaliplatin plus a fluoropyrimidine or paclitaxel in randomized trials include camrelizumab (ESCORT-1$^{st}$) [65], sintilimab (ORIENT-15) [63], tislelizumab (RATIONALE-306) [61], and toripalimab (JUPITER-06) [64].

## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Gastric cancer" and "Society guideline links: Esophageal cancer".)

## INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5$^{th}$ to 6$^{th}$ grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10$^{th}$ to 12$^{th}$ grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Esophageal cancer (The Basics)" and "Patient education: Stomach cancer (The Basics)")

## SUMMARY AND RECOMMENDATIONS

- **Goals of therapy** – In patients with advanced unresectable and metastatic gastric, gastroesophageal junction (GEJ), and esophageal cancer, the goals of systemic therapy include palliating symptoms, improving quality of life, and prolonging survival. (See 'Goals of therapy' above.)

- **Supportive care** – All patients should have a full assessment of symptom burden, and social supports prior to starting chemotherapy. Early referral and initiation of interdisciplinary and palliative care services improve outcomes. (See 'Early supportive care' above.)

- **Biomarker assessment** – Biomarker are used to guide initial management (see 'Biomarker assessment' above):

  - All patients, regardless of histology, should have their tumors assayed for mismatch repair deficiency (dMMR), high levels of microsatellite instability (MSI-H), and programmed cell death ligand 1 (PD-L1) expression using a combined positive score (CPS). (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Tumor MSI/IHC testing' and 'PD-L1 expression status in upper GI tract cancers' above and "Principles of cancer immunotherapy", section on 'Diagnostic tests'.)

  - All patients with gastric or GEJ adenocarcinoma who are eligible for trastuzumab should have their tumors assayed for human epidermal growth factor receptor 2 (HER2) overexpression and/or gene amplification using specific criteria developed for these tumors ( table 1 and algorithm 2). (See 'Assessing HER2 status' above.)

- **Treatment selection** – Our general approach to initial systemic therapy is based on biomarker expression and histology ( algorithm 1).

- **dMMR/MSI-H tumors** – For patients with dMMR/MSI-H metastatic esophageal and gastric cancer (either squamous cell carcinoma [SCC] or adenocarcinoma), we

recommend the addition of an immune checkpoint inhibitor (ICI) to chemotherapy (**Grade 1B**), as this approach improves OS and can induce durable treatment responses. Immunotherapy alone (nivolumab plus ipilimumab or pembrolizumab monotherapy) is an acceptable alternative. Although data are lacking to guide selection of therapy, we suggest initial therapy with FOLFOX plus nivolumab (**Grade 2C**), followed by maintenance therapy for patients without disease progression. (See 'Mismatch repair deficient/MSI-H tumors' above.)

- **SCC** – For patients with advanced SCCs and high PD-L1 expression (TPS ≥1 percent or CPS ≥10), we suggest first-line therapy with chemotherapy plus immunotherapy rather than chemotherapy alone (**Grade 2B**).

  For those whose tumors have low PD-L1 expression, we also suggest chemotherapy plus immunotherapy rather than chemotherapy alone (**Grade 2C**) given the survival benefits in a meta-analysis. However, we have a lower threshold to omit or discontinue immunotherapy in this population due to unfavorable features, as the likelihood of benefit is lower in such patients. We do not favor immunotherapy alone due to concerns about early progression/death compared with chemotherapy alone. (See 'Squamous cell cancers' above.)

  Although some clinical trials use cisplatin plus fluorouracil (FU)-based chemotherapy, we prefer pembrolizumab or nivolumab in combination with an oxaliplatin-based regimen, such as oxaliplatin plus leucovorin with bolus plus short-term FU (FOLFOX, ( table 6)). Where available (mainly China), camrelizumab in combination with paclitaxel and cisplatin is an appropriate alternative. (See 'Selection of the chemotherapy backbone for combined therapy' above.)

- **Gastric and GEJ adenocarcinoma** – For patients with gastric or GEJ adenocarcinoma, we suggest a chemotherapy backbone including both a fluoropyrimidine and oxaliplatin, rather than other chemotherapy combinations (**Grade 2C**). Options include FOLFOX ( table 2) or CAPOX/XELOX ( table 3). (See 'Combination chemotherapy' above.)

  Additional therapy is guided by tumor HER2 status and level of PD-L1 expression:

  - **HER2-positive adenocarcinoma** – For patients with HER2-positive adenocarcinomas, we suggest the addition of trastuzumab (**Grade 2B**) to

chemotherapy. Preferred options include FOLFOX plus trastuzumab ( table 6) and CAPOX plus trastuzumab ( table 7). (See 'Trastuzumab plus chemotherapy' above.)

Additionally, for HER2-positive cancers that also have CPS ≥1, we suggest the addition of pembrolizumab to trastuzumab and chemotherapy (**Grade 2B**). Preferred options include pembrolizumab plus FOLFOX and trastuzumab ( table 8) and pembrolizumab plus CAPOX and trastuzumab ( table 9). (See 'Pembrolizumab plus trastuzumab and chemotherapy' above.)

For patients who are ineligible for trastuzumab ( table 4), we offer an initial treatment approach similar to those with HER2-negative adenocarcinoma. (See 'Ineligible for trastuzumab' above.)

- **HER2-negative adenocarcinoma** – For patients with HER2-negative adenocarcinomas and CPS ≥10, we recommend the addition of either nivolumab or pembrolizumab to chemotherapy (**Grade 1B**) as this approach improved overall survival (OS) in randomized trials. (See 'CPS of 10 or more' above.)

  For patients with HER2-negative adenocarcinomas and CPS of 5 to less than 10, we suggest the addition of nivolumab to chemotherapy (**Grade 2B**). (See 'CPS of 5 to less than 10' above.)

  For HER2-negative adenocarcinoma with CPS <5 and mismatch repair proficiency, we do not incorporate immunotherapy, given that the benefits are less clear in this population and may not outweigh the risks. Such patients are treated with chemotherapy alone. (See 'CPS of less than 5' above.)

- **No molecular marker or contraindication to targeted therapy** – The benefits of immunotherapy are uncertain for adenocarcinomas with no PD-L1 expression and mismatch repair proficiency. Although opinion differs, we suggest initial chemotherapy alone rather than immunotherapy plus chemotherapy in these patients (**Grade 2C**). (See 'CPS of less than 5' above.)

  The choice of regimen is empiric. In general, combination regimens provide higher response rates but only modestly longer disease control and survival. (See 'Combination chemotherapy' above.)

For patients who are candidates for aggressive therapy, we suggest a fluoropyrimidine-containing doublet rather than a triplet regimen (**Grade 2B**). For most patients, we prefer FOLFOX ( table 2), XELOX/CAPOX ( table 3), or, where available, S-1 plus oxaliplatin. Other reasonable options include FU plus cisplatin or S-1 plus cisplatin. (See 'Is there an optimal combination regimen?' above and 'Oxaliplatin combinations' above and 'Cisplatin plus a fluoropyrimidine' above.)

For older patients and those with a poor performance status or significant comorbidity, we would choose leucovorin-modulated FU alone or single-agent capecitabine. Other reasonable options are single-agent irinotecan, low-dose weekly taxanes, or dose-attenuated XELOX/CAPOX. (See 'Single-agent chemotherapy' above and 'Chemotherapy dosing in older and frail patients' above.)

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### REFERENCES

1. SEER Cancer Statistics http://www.seer.cancer.gov/statistics/ (Accessed on March 31, 2011).
2. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 1998; 83:2049.
3. Salvon-Harman JC, Cady B, Nikulasson S, et al. Shifting proportions of gastric adenocarcinomas. Arch Surg 1994; 129:381.
4. Wijnhoven BP, Siersema PD, Hop WC, et al. Adenocarcinomas of the distal oesophagus and gastric cardia are one clinical entity. Rotterdam Oesophageal Tumour Study Group. Br J Surg 1999; 86:529.
5. Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in

advanced esophagogastric cancer. J Clin Oncol 1997; 15:261.

6. Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) With epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol 2002; 20:1996.
7. Chau I, Norman AR, Cunningham D, et al. The impact of primary tumour origins in patients with advanced oesophageal, oesophago-gastric junction and gastric adenocarcinoma--individual patient data from 1775 patients in four randomised controlled trials. Ann Oncol 2009; 20:885.
8. Ilson DH, Wadleigh RG, Leichman LP, Kelsen DP. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. Ann Oncol 2007; 18:898.
9. Muro K, Hamaguchi T, Ohtsu A, et al. A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer. Ann Oncol 2004; 15:955.
10. Einzig AI, Neuberg D, Remick SC, et al. Phase II trial of docetaxel (Taxotere) in patients with adenocarcinoma of the upper gastrointestinal tract previously untreated with cytotoxic chemotherapy: the Eastern Cooperative Oncology Group (ECOG) results of protocol E1293. Med Oncol 1996; 13:87.
11. Ilson DH, Ajani J, Bhalla K, et al. Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the esophagus. J Clin Oncol 1998; 16:1826.
12. Petrasch S, Welt A, Reinacher A, et al. Chemotherapy with cisplatin and paclitaxel in patients with locally advanced, recurrent or metastatic oesophageal cancer. Br J Cancer 1998; 78:511.
13. Wang K, Johnson A, Ali SM, et al. Comprehensive Genomic Profiling of Advanced Esophageal Squamous Cell Carcinomas and Esophageal Adenocarcinomas Reveals Similarities and Differences. Oncologist 2015; 20:1132.
14. Pyrhönen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer 1995; 71:587.
15. Glimelius B, Ekström K, Hoffman K, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol 1997; 8:163.

16. Wagner AD, Grothe W, Haerting J, et al. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 2006; 24:2903.
17. Ter Veer E, Haj Mohammad N, van Valkenhoef G, et al. The Efficacy and Safety of First-line Chemotherapy in Advanced Esophagogastric Cancer: A Network Meta-analysis. J Natl Cancer Inst 2016; 108.
18. Wagner AD, Syn NL, Moehler M, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2017; 8:CD004064.
19. Janmaat VT, Steyerberg EW, van der Gaast A, et al. Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer. Cochrane Database Syst Rev 2017; 11:CD004063.
20. van Kleef JJ, Ter Veer E, van den Boorn HG, et al. Quality of Life During Palliative Systemic Therapy for Esophagogastric Cancer: Systematic Review and Meta-Analysis. J Natl Cancer Inst 2020; 112:12.
21. Attar A, Malka D, Sabaté JM, et al. Malnutrition is high and underestimated during chemotherapy in gastrointestinal cancer: an AGEO prospective cross-sectional multicenter study. Nutr Cancer 2012; 64:535.
22. Anandavadivelan P, Lagergren P. Cachexia in patients with oesophageal cancer. Nat Rev Clin Oncol 2016; 13:185.
23. Kim GM, Kim SJ, Song SK, et al. Prevalence and prognostic implications of psychological distress in patients with gastric cancer. BMC Cancer 2017; 17:283.
24. Arends J. Struggling with nutrition in patients with advanced cancer: nutrition and nourishment-focusing on metabolism and supportive care. Ann Oncol 2018; 29:ii27.
25. Lu Z, Fang Y, Liu C, et al. Early Interdisciplinary Supportive Care in Patients With Previously Untreated Metastatic Esophagogastric Cancer: A Phase III Randomized Controlled Trial. J Clin Oncol 2021; 39:748.
26. Chakravarty D, Johnson A, Sklar J, et al. Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion. J Clin Oncol 2022; 40:1231.
27. Yamashita K, Iwatsuki M, Harada K, et al. Prognostic impacts of the combined positive score and the tumor proportion score for programmed death ligand-1 expression by double immunohistochemical staining in patients with advanced gastric cancer.

Gastric Cancer 2020; 23:95.

28. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228.
29. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92:205.
30. Park SR, Kim MJ, Nam BH, et al. A randomised phase II study of continuous versus stop-and-go S-1 plus oxaliplatin following disease stabilisation in first-line chemotherapy in patients with metastatic gastric cancer. Eur J Cancer 2017; 83:32.
31. Kulangara K, Zhang N, Corigliano E, et al. Clinical Utility of the Combined Positive Score for Programmed Death Ligand-1 Expression and the Approval of Pembrolizumab for Treatment of Gastric Cancer. Arch Pathol Lab Med 2019; 143:330.
32. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015; 372:320.
33. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015; 16:375.
34. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015; 373:23.
35. Weber JS, Kudchadkar RR, Yu B, et al. Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naive melanoma. J Clin Oncol 2013; 31:4311.
36. Doki Y, Ajani JA, Kato K, et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. N Engl J Med 2022; 386:449.
37. FDA List of cleared or approved companion diagnostic devices (in vitro and imaging t ools) https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approve d-companion-diagnostic-devices-in-vitro-and-imaging-tools (Accessed on February 1 5, 2022).
38. Ahn S, Kim KM. PD-L1 expression in gastric cancer: interchangeability of 22C3 and 28-8 pharmDx assays for responses to immunotherapy. Mod Pathol 2021; 34:1719.
39. Kim SW, Jeong G, Ryu MH, Park YS. Comparison of PD-L1 immunohistochemical assays in advanced gastric adenocarcinomas using endoscopic biopsy and paired

resected specimens. Pathology 2021; 53:586.

40. Zhou KI, Peterson B, Serritella A, et al. Spatial and Temporal Heterogeneity of PD-L1 Expression and Tumor Mutational Burden in Gastroesophageal Adenocarcinoma at Baseline Diagnosis and after Chemotherapy. Clin Cancer Res 2020; 26:6453.
41. Catenacci DVT, Moya S, Lomnicki S, et al. Personalized Antibodies for Gastroesophageal Adenocarcinoma (PANGEA): A Phase II Study Evaluating an Individualized Treatment Strategy for Metastatic Disease. Cancer Discov 2021; 11:308.
42. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 2021; 398:27.
43. Shitara K, Ajani JA, Moehler M, et al. Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. Nature 2022; 603:942.
44. Janjigian YY, Ajani JA, Moehler M, et al. First-Line Nivolumab Plus Chemotherapy for Advanced Gastric, Gastroesophageal Junction, and Esophageal Adenocarcinoma: 3-Year Follow-Up of the Phase III CheckMate 649 Trial. J Clin Oncol 2024; 42:2012.
45. Rha SY, Oh DY, Yañez P, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2023; 24:1181.
46. Moehler M, Xiao H, Blum SI, et al. Health-Related Quality of Life With Nivolumab Plus Chemotherapy Versus Chemotherapy in Patients With Advanced Gastric/Gastroesophageal Junction Cancer or Esophageal Adenocarcinoma From CheckMate 649. J Clin Oncol 2023; 41:5388.
47. DailyMed Drug Information: https://dailymed.nlm.nih.gov/dailymed/index.cfm (Accessed on July 01, 2024).
48. https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo (Accessed on March 09, 2022).
49. Zhao JJ, Yap DWT, Chan YH, et al. Low Programmed Death-Ligand 1-Expressing Subgroup Outcomes of First-Line Immune Checkpoint Inhibitors in Gastric or Esophageal Adenocarcinoma. J Clin Oncol 2022; 40:392.
50. Shitara K, Van Cutsem E, Bang YJ, et al. Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-

line, Advanced Gastric Cancer: The KEYNOTE-062 Phase 3 Randomized Clinical Trial. JAMA Oncol 2020; 6:1571.

51. Kang YK, Chen LT, Ryu MH, et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2022; 23:234.
52. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet 2021; 398:759.
53. Metges J-P, Kato K, Sun J-M, et al. First-line pembrolizumab plus chemotherapy versus chemotherapy in advanced esophageal cancer: Longer-term efficacy, safety, and quality-of-life results from the phase 3 KEYNOTE-590 study (abstract). J Clin Oncol 2022.40. 4_suppl.241. Abstract available online at https://meetinglibrary.asco.org/record/204509/abstract (Accessed on February 15, 2022).
54. Opdivo, INN-nivolumab. European Medicines Agency. Available at: https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf (Accessed on June 15, 2022).
55. Yoon HH, Dong H, Shi Q. Impact of PD-1 Blockade in Nonresponders: Pitfalls and Promise. Clin Cancer Res 2022; 28:3173.
56. OPDIVO- nivolumab injection, prescribing information. DailyMed. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f570b9c4-6846-4de2-abfa-4d0a4ae4e394 (Accessed on June 15, 2022).
57. YERVOY- ipilimumab injection, prescribing information. DailyMed. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2265ef30-253e-11df-8a39-0800200c9a66 (Accessed on June 15, 2022).
58. FDA approves pembrolizumab for esophageal or GEJ carcinoma. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-esophageal-or-gej-carcinoma?utm_medium=email&utm_source=govdelivery (Accessed on March 23, 2021).
59. https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda (Accessed on March 09, 2022).

60. Yap DWT, Leone AG, Wong NZH, et al. Effectiveness of Immune Checkpoint Inhibitors in Patients With Advanced Esophageal Squamous Cell Carcinoma: A Meta-analysis Including Low PD-L1 Subgroups. JAMA Oncol 2023; 9:215.
61. Xu J, Kato K, Raymond E, et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced or metastatic oesophageal squamous cell carcinoma (RATIONALE-306): a global, randomised, placebo-controlled, phase 3 study. Lancet Oncol 2023; 24:483.
62. Yoon HH, Jin Z, Kour O, et al. Association of PD-L1 Expression and Other Variables With Benefit From Immune Checkpoint Inhibition in Advanced Gastroesophageal Cancer: Systematic Review and Meta-analysis of 17 Phase 3 Randomized Clinical Trials. JAMA Oncol 2022; 8:1456.
63. Lu Z, Wang J, Shu Y, et al. Sintilimab versus placebo in combination with chemotherapy as first line treatment for locally advanced or metastatic oesophageal squamous cell carcinoma (ORIENT-15): multicentre, randomised, double blind, phase 3 trial. BMJ 2022; 377:e068714.
64. Wang ZX, Cui C, Yao J, et al. Toripalimab plus chemotherapy in treatment-naïve, advanced esophageal squamous cell carcinoma (JUPITER-06): A multi-center phase 3 trial. Cancer Cell 2022; 40:277.
65. Luo H, Lu J, Bai Y, et al. Effect of Camrelizumab vs Placebo Added to Chemotherapy on Survival and Progression-Free Survival in Patients With Advanced or Metastatic Esophageal Squamous Cell Carcinoma: The ESCORT-1st Randomized Clinical Trial. JAMA 2021; 326:916.
66. Wu HX, Pan YQ, He Y, et al. Clinical Benefit of First-Line Programmed Death-1 Antibody Plus Chemotherapy in Low Programmed Cell Death Ligand 1-Expressing Esophageal Squamous Cell Carcinoma: A Post Hoc Analysis of JUPITER-06 and Meta-Analysis. J Clin Oncol 2023; 41:1735.
67. Chao J, Fuchs CS, Shitara K, et al. Assessment of Pembrolizumab Therapy for the Treatment of Microsatellite Instability-High Gastric or Gastroesophageal Junction Cancer Among Patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 Clinical Trials. JAMA Oncol 2021; 7:895.
68. Bang YJ, Van Cutsem E, Feyereislova A, et al. 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 2010; 376:687.

69. Ter Veer E, Creemers A, de Waal L, et al. Comparing cytotoxic backbones for first-line trastuzumab-containing regimens in human epidermal growth factor receptor 2-positive advanced oesophagogastric cancer: A meta-analysis. Int J Cancer 2018; 143:438.
70. Janjigian YY, Maron SB, Chatila WK, et al. First-line pembrolizumab and trastuzumab in HER2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: an open-label, single-arm, phase 2 trial. Lancet Oncol 2020; 21:821.
71. Lee CK, Rha SY, Kim HS, et al. A single arm phase Ib/II trial of first-line pembrolizumab, trastuzumab and chemotherapy for advanced HER2-positive gastric cancer. Nat Commun 2022; 13:6002.
72. Janjigian YY, Kawazoe A, Bai Y, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. Lancet 2023; 402:2197.
73. Janjigian YY, Kawazoe A, Yañez P, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. Nature 2021; 600:727.
74. Hecht JR, Bang YJ, Qin SK, et al. Lapatinib in Combination With Capecitabine Plus Oxaliplatin in Human Epidermal Growth Factor Receptor 2-Positive Advanced or Metastatic Gastric, Esophageal, or Gastroesophageal Adenocarcinoma: TRIO-013/LOGiC--A Randomized Phase III Trial. J Clin Oncol 2016; 34:443.
75. Tabernero J, Hoff PM, Shen L, et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Lancet Oncol 2018; 19:1372.
76. Park H, Jin RU, Wang-Gillam A, et al. FOLFIRINOX for the Treatment of Advanced Gastroesophageal Cancers: A Phase 2 Nonrandomized Clinical Trial. JAMA Oncol 2020; 6:1231.
77. Lordick F, Kang YK, Chung HC, et al. 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 2013; 14:490.
78. Waddell T, Chau I, Cunningham D, et al. 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 2013; 14:481.

79. Van Cutsem E, de Haas S, Kang YK, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a biomarker evaluation from the AVAGAST randomized phase III trial. J Clin Oncol 2012; 30:2119.
80. Gordon MA, Gundacker HM, Benedetti J, et al. Assessment of HER2 gene amplification in adenocarcinomas of the stomach or gastroesophageal junction in the INT-0116/SWOG9008 clinical trial. Ann Oncol 2013; 24:1754.
81. Terashima M, Kitada K, Ochiai A, et al. Impact of expression of human epidermal growth factor receptors EGFR and ERBB2 on survival in stage II/III gastric cancer. Clin Cancer Res 2012; 18:5992.
82. Janjigian YY, Werner D, Pauligk C, et al. Prognosis of metastatic gastric and gastroesophageal junction cancer by HER2 status: a European and USA International collaborative analysis. Ann Oncol 2012; 23:2656.
83. Okines AF, Thompson LC, Cunningham D, et al. Effect of HER2 on prognosis and benefit from peri-operative chemotherapy in early oesophago-gastric adenocarcinoma in the MAGIC trial. Ann Oncol 2013; 24:1253.
84. Lordick F, Kang YK, Salman P, et al. Clinical outcome according to tumor HER2 status and EGFR expression in advanced gastric cancer patients from the EXPAND study. J Clin Oncol 2013; 31S: ASCO #4021.
85. Chua TC, Merrett ND. Clinicopathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes--a systematic review. Int J Cancer 2012; 130:2845.
86. Yoon HH, Shi Q, Sukov WR, et al. Association of HER2/ErbB2 expression and gene amplification with pathologic features and prognosis in esophageal adenocarcinomas. Clin Cancer Res 2012; 18:546.
87. Schoppmann SF, Jesch B, Friedrich J, et al. Expression of Her-2 in carcinomas of the esophagus. Am J Surg Pathol 2010; 34:1868.
88. Hu Y, Bandla S, Godfrey TE, et al. HER2 amplification, overexpression and score criteria in esophageal adenocarcinoma. Mod Pathol 2011; 24:899.
89. Brien TP, Odze RD, Sheehan CE, et al. HER-2/neu gene amplification by FISH predicts

poor survival in Barrett's esophagus-associated adenocarcinoma. Hum Pathol 2000; 31:35.

90. Thompson SK, Sullivan TR, Davies R, Ruszkiewicz AR. Her-2/neu gene amplification in esophageal adenocarcinoma and its influence on survival. Ann Surg Oncol 2011; 18:2010.
91. Reichelt U, Duesedau P, Tsourlakis MCh, et al. Frequent homogeneous HER-2 amplification in primary and metastatic adenocarcinoma of the esophagus. Mod Pathol 2007; 20:120.
92. Custodio A, Carmona-Bayonas A, Jiménez-Fonseca P, et al. Nomogram-based prediction of survival in patients with advanced oesophagogastric adenocarcinoma receiving first-line chemotherapy: a multicenter prospective study in the era of trastuzumab. Br J Cancer 2017; 116:1526.
93. Ajani JA, Ilson DH, Daugherty K, et al. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. J Natl Cancer Inst 1994; 86:1086.
94. Mavroudis D, Kourousis C, Androulakis N, et al. Frontline treatment of advanced gastric cancer with docetaxel and granulocyte colony-stimulating factor (G-CSF): a phase II trial. Am J Clin Oncol 2000; 23:341.
95. Sulkes A, Smyth J, Sessa C, et al. Docetaxel (Taxotere) in advanced gastric cancer: results of a phase II clinical trial. EORTC Early Clinical Trials Group. Br J Cancer 1994; 70:380.
96. Kato K, Tahara M, Hironaka S, et al. A phase II study of paclitaxel by weekly 1-h infusion for advanced or recurrent esophageal cancer in patients who had previously received platinum-based chemotherapy. Cancer Chemother Pharmacol 2011; 67:1265.
97. Kii T, Takiuchi H, Gotoh M, et al. [Weekly administration regimen of paclitaxel (PTX) in patient with inoperable or recurrent gastric cancer]. Gan To Kagaku Ryoho 2006; 33:621.
98. Köhne CH, Catane R, Klein B, et al. Irinotecan is active in chemonaive patients with metastatic gastric cancer: a phase II multicentric trial. Br J Cancer 2003; 89:997.
99. Enzinger PC, Kulke MH, Clark JW, et al. A phase II trial of irinotecan in patients with previously untreated advanced esophageal and gastric adenocarcinoma. Dig Dis Sci 2005; 50:2218.

100. Kok TC, van der Gaast A, Splinter TA. 5-fluorouracil and folinic acid in advanced adenocarcinoma of the esophagus or esophago-gastric junction area. Rotterdam Esophageal Tumor Study Group. Ann Oncol 1996; 7:533.

101. Alberts AS, Schoeman L, Burger W, et al. A phase II study of 5-fluorouracil and leucovorin in advanced carcinoma of the esophagus. Am J Clin Oncol 1992; 15:35.

102. Hara H, Kadowaki S, Asayama M, et al. First-line bolus 5-fluorouracil plus leucovorin for peritoneally disseminated gastric cancer with massive ascites or inadequate oral intake. Int J Clin Oncol 2018; 23:275.

103. Hong YS, Song SY, Lee SI, et al. A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. Ann Oncol 2004; 15:1344.

104. Koizumi W, Saigenji K, Ujiie S, et al. A pilot phase II study of capecitabine in advanced or recurrent gastric cancer. Oncology 2003; 64:232.

105. Shirasaka T, Shimamato Y, Ohshimo H, et al. Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs 1996; 7:548.

106. van Groeningen CJ, Peters GJ, Schornagel JH, et al. Phase I clinical and pharmacokinetic study of oral S-1 in patients with advanced solid tumors. J Clin Oncol 2000; 18:2772.

107. Boku N, Yamamoto S, Fukuda H, et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol 2009; 10:1063.

108. Lee JL, Kang YK, Kang HJ, et al. A randomised multicentre phase II trial of capecitabine vs S-1 as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. Br J Cancer 2008; 99:584.

109. Lee SJ, Cho SH, Yoon JY, et al. Phase II study of S-1 monotherapy in paclitaxel- and cisplatin-refractory gastric cancer. Cancer Chemother Pharmacol 2009; 65:159.

110. Jeung HC, Rha SY, Shin SJ, et al. A phase II study of S-1 monotherapy administered for 2 weeks of a 3-week cycle in advanced gastric cancer patients with poor performance status. Br J Cancer 2007; 97:458.

111. Chu MP, Hecht JR, Slamon D, et al. Association of Proton Pump Inhibitors and Capecitabine Efficacy in Advanced Gastroesophageal Cancer: Secondary Analysis of

the TRIO-013/LOGiC Randomized Clinical Trial. JAMA Oncol 2017; 3:767.

112. Sun J, Ilich AI, Kim CA, et al. Concomitant Administration of Proton Pump Inhibitors and Capecitabine is Associated With Increased Recurrence Risk in Early Stage Colorectal Cancer Patients. Clin Colorectal Cancer 2016; 15:257.
113. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 2008; 9:215.
114. Koizumi W, Kim YH, Fujii M, et al. Addition of docetaxel to S-1 without platinum prolongs survival of patients with advanced gastric cancer: a randomized study (START). J Cancer Res Clin Oncol 2014; 140:319.
115. Al-Batran SE, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008; 26:1435.
116. van Meerten E, Eskens FA, van Gameren EC, et al. First-line treatment with oxaliplatin and capecitabine in patients with advanced or metastatic oesophageal cancer: a phase II study. Br J Cancer 2007; 96:1348.
117. Louvet C, André T, Tigaud JM, et al. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. J Clin Oncol 2002; 20:4543.
118. Al-Batran SE, Atmaca A, Hegewisch-Becker S, et al. Phase II trial of biweekly infusional fluorouracil, folinic acid, and oxaliplatin in patients with advanced gastric cancer. J Clin Oncol 2004; 22:658.
119. Jatoi A, Murphy BR, Foster NR, et al. Oxaliplatin and capecitabine in patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia: a phase II study from the North Central Cancer Treatment Group. Ann Oncol 2006; 17:29.
120. Park YH, Kim BS, Ryoo BY, Yang SH. A phase II study of capecitabine plus 3-weekly oxaliplatin as first-line therapy for patients with advanced gastric cancer. Br J Cancer 2006; 94:959.
121. Neri B, Pantaleo P, Giommoni E, et al. Oxaliplatin, 5-fluorouracil/leucovorin and epirubicin as first-line treatment in advanced gastric carcinoma: a phase II study. Br J

Cancer 2007; 96:1043.

122. Liu ZF, Guo QS, Zhang XQ, et al. Biweekly oxaliplatin in combination with continuous infusional 5-fluorouracil and leucovorin (modified FOLFOX-4 regimen) as first-line chemotherapy for elderly patients with advanced gastric cancer. Am J Clin Oncol 2008; 31:259.
123. Di Lauro L, Nunziata C, Arena MG, et al. Irinotecan, docetaxel and oxaliplatin combination in metastatic gastric or gastroesophageal junction adenocarcinoma. Br J Cancer 2007; 97:593.
124. Kim GM, Jeung HC, Rha SY, et al. A randomized phase II trial of S-1-oxaliplatin versus capecitabine-oxaliplatin in advanced gastric cancer. Eur J Cancer 2012; 48:518.
125. Wang J, Chang J, Yu H, et al. A phase II study of oxaliplatin in combination with leucovorin and fluorouracil as first-line chemotherapy in patients with metastatic squamous cell carcinoma of esophagus. Cancer Chemother Pharmacol 2013; 71:905.
126. Van Cutsem E, Boni C, Tabernero J, et al. Docetaxel plus oxaliplatin with or without fluorouracil or capecitabine in metastatic or locally recurrent gastric cancer: a randomized phase II study. Ann Oncol 2015; 26:149.
127. Al-Batran SE, Pauligk C, Homann N, et al. The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65+). Eur J Cancer 2013; 49:835.
128. Enzinger PC, Burtness BA, Niedzwiecki D, et al. CALGB 80403 (Alliance)/E1206: A Randomized Phase II Study of Three Chemotherapy Regimens Plus Cetuximab in Metastatic Esophageal and Gastroesophageal Junction Cancers. J Clin Oncol 2016; 34:2736.
129. Enzinger PC, Burtness B, Hollis D, et al. CALGB 80403/ECOG 1206: A randomized phase II study of three standard chemotherapy regimens (ECF, IC, FOLFOX) plus cetuximab in metastatic esophageal and GE junction cancer. J Clin Oncol 2010; 28S: ASCO #4006.
130. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358:36.
131. Yamada Y, Higuchi K, Nishikawa K, et al. Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer.

Ann Oncol 2015; 26:141.

132. Kang YK, Chin K, Chung HC, et al. S-1 plus leucovorin and oxaliplatin versus S-1 plus cisplatin as first-line therapy in patients with advanced gastric cancer (SOLAR): a randomised, open-label, phase 3 trial. Lancet Oncol 2020; 21:1045.
133. Xu R-H, Wang Z-Q, Shen L, et al. S-1 plus oxaliplatin versus S-1 plus cisplatin as first-line treatment for advanced diffuse-type or mixed-type gastric/gastroesophageal junction adenocarcinoma: A randomized, phase 3 trial. J Clin Oncol 2019; 37S: ASCO #4017.
134. Popov I, Radosevic-Jelic L, Jezdic S, et al. Biweekly oxaliplatin, fluorouracil and leucovorin versus cisplatin, fluorouracil and leucovorin in patients with advanced gastric cancer. J BUON 2008; 13:505.
135. Montagnani F, Turrisi G, Marinozzi C, et al. Effectiveness and safety of oxaliplatin compared to cisplatin for advanced, unresectable gastric cancer: a systematic review and meta-analysis. Gastric Cancer 2011; 14:50.
136. Bleiberg H, Conroy T, Paillot B, et al. Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. Eur J Cancer 1997; 33:1216.
137. Warner E, Jensen JL, Cripps C, et al. Outpatient 5-fluorouracil, folinic acid and cisplatin in patients with advanced esophageal carcinoma. Acta Oncol 1999; 38:255.
138. Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol 2009; 20:666.
139. Okines AF, Norman AR, McCloud P, et al. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Ann Oncol 2009; 20:1529.
140. Jin M, Lu H, Li J, et al. Ramdomized 3-armed phase III study of S-1 monotherapy versus S-1/CDDP (SP) versus 5-FU/CDDP (FP) in patients (pts) with advanced gastric cancer (AGC): SC-101 study. J Clin Oncol 2008; 26S: ASCO #4533.
141. Nishikawa K, Tsuburaya A, Yoshikawa T, et al. A randomised phase II trial of capecitabine plus cisplatin versus S-1 plus cisplatin as a first-line treatment for advanced gastric cancer: Capecitabine plus cisplatin ascertainment versus S-1 plus

cisplatin randomised PII trial (XParTS II). Eur J Cancer 2018; 101:220.

142. Ajani JA, Lee FC, Singh DA, et al. Multicenter phase II trial of S-1 plus cisplatin in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol 2006; 24:663.
143. Lenz HJ, Lee FC, Haller DG, et al. Extended safety and efficacy data on S-1 plus cisplatin in patients with untreated, advanced gastric carcinoma in a multicenter phase II study. Cancer 2007; 109:33.
144. Ajani JA, Rodriguez W, Bodoky G, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol 2010; 28:1547.
145. Ajani JA, Buyse M, Lichinitser M, et al. Combination of cisplatin/S-1 in the treatment of patients with advanced gastric or gastroesophageal adenocarcinoma: Results of noninferiority and safety analyses compared with cisplatin/5-fluorouracil in the First-Line Advanced Gastric Cancer Study. Eur J Cancer 2013; 49:3616.
146. Ajani JA, Abramov M, Bondarenko I, et al. A phase III trial comparing oral S-1/cisplatin and intravenous 5-fluorouracil/cisplatin in patients with untreated diffuse gastric cancer. Ann Oncol 2017; 28:2142.
147. Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2010; :CD004064.
148. Bouché O, Raoul JL, Bonnetain F, et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study--FFCD 9803. J Clin Oncol 2004; 22:4319.
149. Oh SC, Sur HY, Sung HJ, et al. A phase II study of biweekly dose-intensified oral capecitabine plus irinotecan (bXELIRI) for patients with advanced or metastatic gastric cancer. Br J Cancer 2007; 96:1514.
150. Moehler M, Kanzler S, Geissler M, et al. A randomized multicenter phase II study comparing capecitabine with irinotecan or cisplatin in metastatic adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol 2010; 21:71.
151. Luo HY, Wang ZQ, Wang FH, et al. Phase 2 study of capecitabine and irinotecan combination chemotherapy (modified XELIRI regimen) in patients with advanced

gastric cancer. Am J Clin Oncol 2011; 34:555.

152. Narahara H, Iishi H, Imamura H, et al. Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). Gastric Cancer 2011; 14:72.
153. Ilson DH. Phase II trial of weekly irinotecan/cisplatin in advanced esophageal cancer. Oncology (Williston Park) 2004; 18:22.
154. Ilson DH, Saltz L, Enzinger P, et al. Phase II trial of weekly irinotecan plus cisplatin in advanced esophageal cancer. J Clin Oncol 1999; 17:3270.
155. Ajani JA, Baker J, Pisters PW, et al. CPT-11 plus cisplatin in patients with advanced, untreated gastric or gastroesophageal junction carcinoma: results of a phase II study. Cancer 2002; 94:641.
156. Shirao K, Shimada Y, Kondo H, et al. Phase I-II study of irinotecan hydrochloride combined with cisplatin in patients with advanced gastric cancer. J Clin Oncol 1997; 15:921.
157. Boku N, Ohtsu A, Shimada Y, et al. Phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer. J Clin Oncol 1999; 17:319.
158. Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French intergroup (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) study. J Clin Oncol 2014; 32:3520.
159. Findlay M, Cunningham D, Norman A, et al. A phase II study in advanced gastro-esophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). Ann Oncol 1994; 5:609.
160. Lutz MP, Wilke H, Wagener DJ, et al. Weekly infusional high-dose fluorouracil (HD-FU), HD-FU plus folinic acid (HD-FU/FA), or HD-FU/FA plus biweekly cisplatin in advanced gastric cancer: randomized phase II trial 40953 of the European Organisation for Research and Treatment of Cancer Gastrointestinal Group and the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2007; 25:2580.
161. Yun J, Lee J, Park SH, et al. A randomised phase II study of combination chemotherapy with epirubicin, cisplatin and capecitabine (ECX) or cisplatin and capecitabine (CX) in

advanced gastric cancer. Eur J Cancer 2010; 46:885.

162. Ridwelski K, Fahlke J, Kettner E, et al. Docetaxel-cisplatin (DC) versus 5-fluorouracil-leucovorin-cisplatin (FLC) as first-line treatment for locally advanced or metastatic gastric cancer: Preliminary results of a phase III study. J Clin Oncol 2008; 26S: ASCO #4512.
163. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, Oba K, Paoletti X, et al. Role of chemotherapy for advanced/recurrent gastric cancer: an individual-patient-data meta-analysis. Eur J Cancer 2013; 49:1565.
164. Yamada Y, Boku N, Mizusawa J, et al. Docetaxel plus cisplatin and S-1 versus cisplatin and S-1 in patients with advanced gastric cancer (JCOG1013): an open-label, phase 3, randomised controlled trial. Lancet Gastroenterol Hepatol 2019; 4:501.
165. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. 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 2006; 24:4991.
166. Roth AD, Fazio N, Stupp R, et al. Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol 2007; 25:3217.
167. Ajani JA, Fodor MB, Tjulandin SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. J Clin Oncol 2005; 23:5660.
168. Thuss-Patience PC, Kretzschmar A, Repp M, et al. Docetaxel and continuous-infusion fluorouracil versus epirubicin, cisplatin, and fluorouracil for advanced gastric adenocarcinoma: a randomized phase II study. J Clin Oncol 2005; 23:494.
169. Takahashi H, Arimura Y, Yamashita K, et al. Phase I/II study of docetaxel/cisplatin/fluorouracil combination chemotherapy against metastatic esophageal squamous cell carcinoma. J Thorac Oncol 2010; 5:122.
170. Park SR, Chun JH, Kim YW, et al. Phase II study of low-dose docetaxel/fluorouracil/cisplatin in metastatic gastric carcinoma. Am J Clin Oncol 2005; 28:433.

171. Park SR, Chun JH, Yu MS, et al. Phase II study of docetaxel and irinotecan combination chemotherapy in metastatic gastric carcinoma. Br J Cancer 2006; 94:1402.

172. Giordano KF, Jatoi A, Stella PJ, et al. Docetaxel and capecitabine in patients with metastatic adenocarcinoma of the stomach and gastroesophageal junction: a phase II study from the North Central Cancer Treatment Group. Ann Oncol 2006; 17:652.

173. Kim JG, Sohn SK, Kim DH, et al. Phase II study of docetaxel and capecitabine in patients with metastatic or recurrent gastric cancer. Oncology 2005; 68:190.

174. Chun JH, Kim HK, Lee JS, et al. Weekly docetaxel in combination with capecitabine in patients with metastatic gastric cancer. Am J Clin Oncol 2005; 28:188.

175. Overman MJ, Kazmi SM, Jhamb J, et al. Weekly docetaxel, cisplatin, and 5-fluorouracil as initial therapy for patients with advanced gastric and esophageal cancer. Cancer 2010; 116:1446.

176. Lorenzen S, Duyster J, Lersch C, et al. Capecitabine plus docetaxel every 3 weeks in first- and second-line metastatic oesophageal cancer: final results of a phase II trial. Br J Cancer 2005; 92:2129.

177. Ajani JA, Moiseyenko VM, Tjulandin S, et al. Clinical benefit with docetaxel plus fluorouracil and cisplatin compared with cisplatin and fluorouracil in a phase III trial of advanced gastric or gastroesophageal cancer adenocarcinoma: the V-325 Study Group. J Clin Oncol 2007; 25:3205.

178. Ajani JA, Moiseyenko VM, Tjulandin S, et al. Quality of life with docetaxel plus cisplatin and fluorouracil compared with cisplatin and fluorouracil from a phase III trial for advanced gastric or gastroesophageal adenocarcinoma: the V-325 Study Group. J Clin Oncol 2007; 25:3210.

179. Kelsen D, Jhawer M, Ilson D, et al. Analysis of survival with modified docetaxel, cisplatin, fluorouracil (mDCF), and bevacizumab (BEV) in patients with metastatic gastroesophageal (GE) adenocarcinoma: Results of a phase II clinical trial. J Clin Oncol 2009; 27S: ASCO #4512.

180. Shah MA, Jhawer M, Ilson DH, et al. Phase II study of modified docetaxel, cisplatin, and fluorouracil with bevacizumab in patients with metastatic gastroesophageal adenocarcinoma. J Clin Oncol 2011; 29:868.

181. Shah MA, Janjigian YY, Stoller R, et al. Randomized Multicenter Phase II Study of Modified Docetaxel, Cisplatin, and Fluorouracil (DCF) Versus DCF Plus Growth Factor

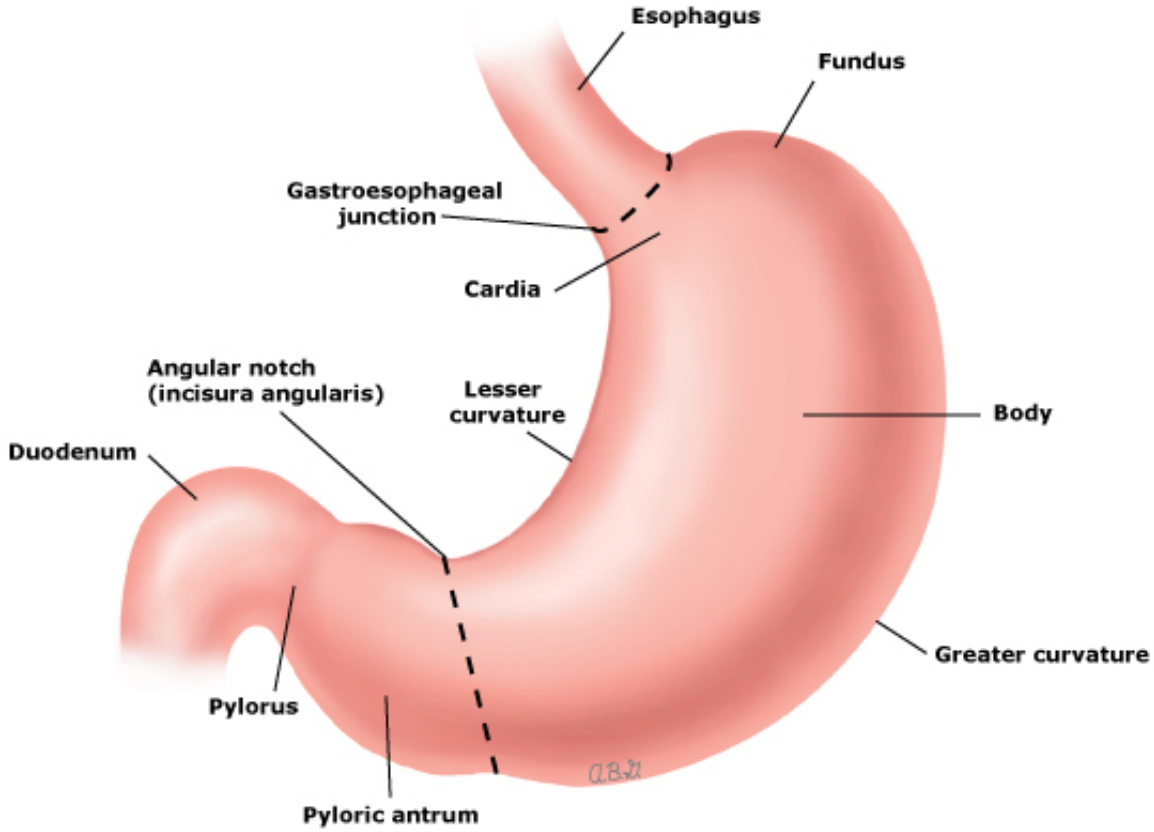
Support in Patients With Metastatic Gastric Adenocarcinoma: A Study of the US Gastric Cancer Consortium. J Clin Oncol 2015; 33:3874.

182. Dijksterhuis WPM, Verhoeven RHA, Slingerland M, et al. Heterogeneity of first-line palliative systemic treatment in synchronous metastatic esophagogastric cancer patients: A real-world evidence study. Int J Cancer 2020; 146:1889.
183. Hall PS, Swinson D, Cairns DA, et al. Efficacy of Reduced-Intensity Chemotherapy With Oxaliplatin and Capecitabine on Quality of Life and Cancer Control Among Older and Frail Patients With Advanced Gastroesophageal Cancer: The GO2 Phase 3 Randomized Clinical Trial. JAMA Oncol 2021; 7:869.
184. Klempner SJ, Lee KW, Shitara K, et al. ILUSTRO: Phase II Multicohort Trial of Zolbetuximab in Patients with Advanced or Metastatic Claudin 18.2-Positive Gastric or Gastroesophageal Junction Adenocarcinoma. Clin Cancer Res 2023; 29:3882.
185. Shitara K, Lordick F, Bang YJ, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. Lancet 2023; 401:1655.
186. Xu R, Shitara K, Ajani JA, et al. Zolbetuximab + CAPOX in 1L claudin-18.2+ (CLDN18.2+)/HER2– locally advanced (LA) or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: Primary phase 3 results from GLOW. J Clin Oncol 2023; 41;36S.
187. Xu J, Jiang H, Pan Y, et al. Sintilimab Plus Chemotherapy for Unresectable Gastric or Gastroesophageal Junction Cancer: The ORIENT-16 Randomized Clinical Trial. JAMA 2023; 330:2064.
188. Moehler MH, Kato K, Arkenau T. Rationale 305: Phase 3 study of tislelizumab plus chemotherapy vs placebo plus chemotherapy as first-line treatment (1L) of advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC). J Clin Oncol 2023; 41;4S.

Topic 2473 Version 128.0

## GRAPHICS

### Parts of the stomach




This drawing shows the parts of the anterior surface of the stomach. The body of the stomach is separated from the pyloric part by an oblique line that extends from the angular notch (incisura angularis) on the lesser curvature to the greater curvature.

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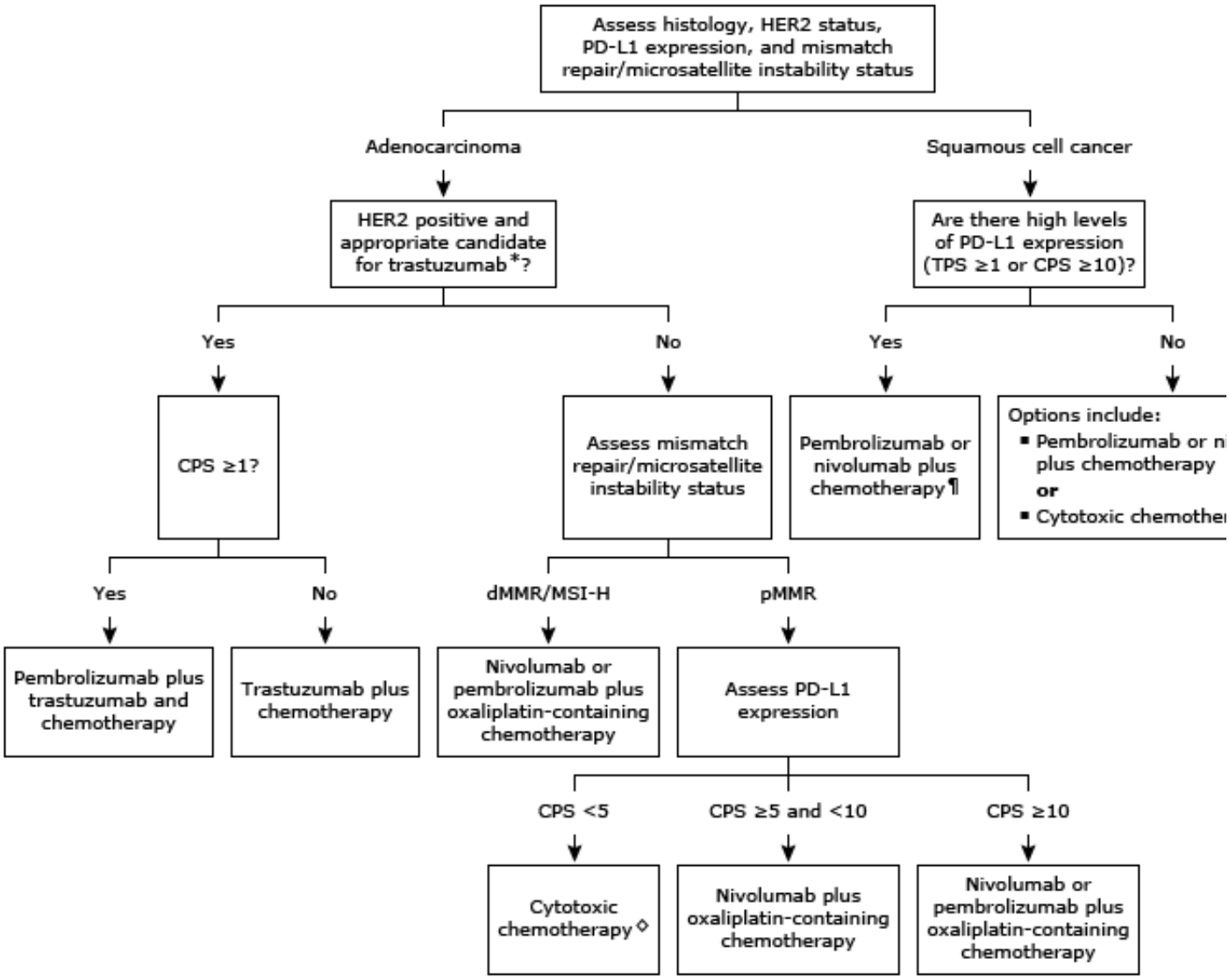
Graphic 79793 Version 4.0

# Initial systemic therapy for advanced and metastatic esophageal and gastric cancer




CAPOX/XELOX: capecitabine plus oxaliplatin; CPS: combined positive score; dMMR: deficient mismatch repair; FOLFOX: oxaliplatin, leucovorin plus bolus and short-term infusional FU; FU: fluorouracil; HER2: human epidermal growth factor receptor 2; MSI-H: microsatellite instability-high; PD-L1: programmed cell death ligand-1; pMMR: proficient mismatch repair; TPS: Tumor Proportion Score.

* Refer to text for guidelines for exclusion of patients for trastuzumab on the basis of excess cardiac risk.

¶ While the chemotherapy backbone in the KEYNOTE-590 trial was cisplatin plus FU many clinicians prefer an oxaliplatin-containing regimen (eg, FOLFOX, CAPOX [XELOX]) in this setting.

Δ Patients with squamous cell carcinoma and low levels of PD-L1 expression can be treated with immunotherapy plus chemotherapy. However, we have a lower threshold to omit or discontinue immunotherapy for unfavorable baseline features (eg, CPS <1, significant non-cancerous lung

disease, experiencing toxicity) than PD-L1 high disease. We do not favor immunotherapy alone due to concerns about early disease progression/death compared with chemotherapy alone.

◇ For patients with HER2-negative esophagogastric adenocarcinoma, mismatch repair proficient disease, and CPS <5, data suggest limited benefit for adding immunotherapy to chemotherapy. However, opinions differ on the use of immunotherapy in this population. Refer to UpToDate content on systemic therapy for esophageal and gastric cancer.

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Graphic 129948 Version 7.0

## Scoring guidelines for the interpretation of HER2 immunohistochemical staining (IHC) in esophagogastric adenocarcinoma

| Surgical specimen-staining pattern | Biopsy specimen-staining pattern | Score | HER2 expression assessment |
|---|---|---|---|
| No reactivity or membranous reactivity in <10% of tumor cells | No reactivity or no membranous reactivity in any tumor cell | 0 | Negative |
| Faint/barely perceptible membranous reactivity in ≥10% of tumor cells; cells are reactive only in part of their membrane | Tumor cell cluster* with a faint/barely perceptible membranous reactivity irrespective of percentage of tumor cells stained | 1+ | Negative |
| Weak to moderate, complete, basolateral or lateral membranous reactivity in ≥10% of tumor cells | Tumor cell cluster* with a weak to moderate, complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained | 2+ | Equivocal |
| Strong, complete, basolateral or lateral membranous reactivity in ≥10% of tumor cells | Tumor cell cluster* with a strong, complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained | 3+ | Positive |

HER2: human epidermal growth factor receptor 2.
* Tumor cell cluster (5 neoplastic cells).

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*Original table published in Hofmann M, Stoss O, Shi D, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology 2008; 52:797. http://onlinelibrary.wiley.com/wol1/doi/10.1111/j.1365-2559.2008.03028.x/abstract. Copyright © 2008. Reproduced with permission of John Wiley & Sons Inc. This image has been provided by or is owned by Wiley. Further permission is needed before it can be downloaded to PowerPoint, printed, shared or emailed. Please contact Wiley's permissions department either via email: permissions@wiley.com or use the RightsLink service by clicking on the 'Request Permission' link accompanying this article on Wiley Online Library (http://onlinelibrary.wiley.com).*
*Modified table reprinted from Bartley AN, Washington MK, Ventura CB, et al. HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology. Arch Pathol Lab Med 2016; 140(12):1345-1363. From Archives of Pathology & Laboratory Medicine. Copyright 2016 College of American Pathologists.*

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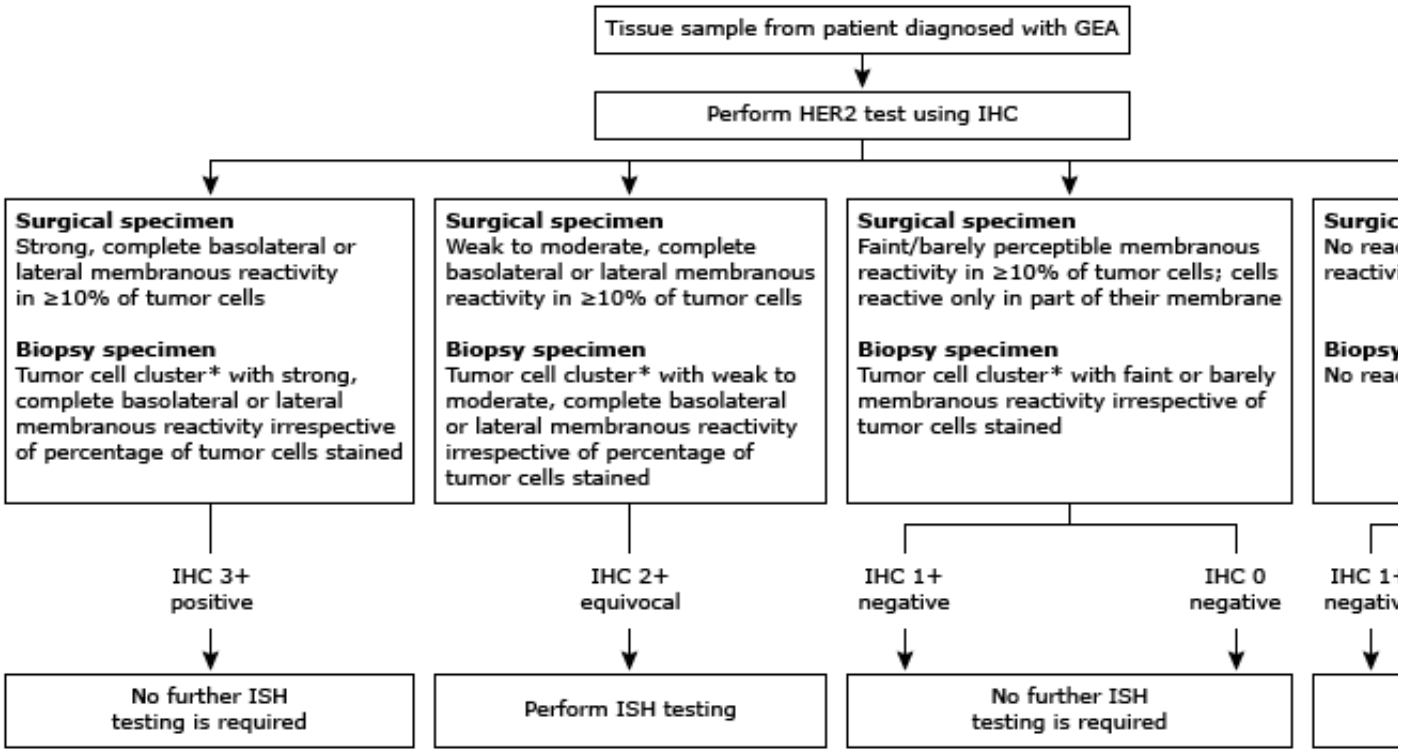
Graphic 110996 Version 1.0

## Algorithm for HER2 testing in advanced gastroesophageal adenocarcinoma




Algorithm for pathologists.
Additional recommendations: Pathologists should ensure that biopsy or resection specimens used for HER2 testing are rapidly placed in fixative, ideally within 1 hour (cold ischemic time), and are fixed in 10% neutral buffered formalin for 6 to 72 hours. Routine histology processing and HER2 testing should be performed according to analytically validated protocols. Pathologists should identify areas of invasive adenocarcinoma and also mark areas with strongest intensity of HER2 expression by IHC in the GEA specimen for subsequent scoring when ISH is required.

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HER2: human epidermal growth factor receptor 2; GEA: gastroesophageal adenocarcinoma; IHC: immunohistochemistry; ISH: in situ hybridization.
* Tumor cell cluster is defined as a cluster of 5 or more tumor cells.

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Graphic 110995 Version 4.0

## Chemotherapy regimens for gastrointestinal cancer: Modified FOLFOX6[1,2]

| **Cycle length:** 14 days. | | | |
|---|---|---|---|
| **Drug** | **Dose and route** | **Administration** | **Given on days** |
| Oxaliplatin | 85 mg/m$^2$ IV* | Dilute with 500 mL D5W¶ and administer over two hours (on days 1 and 15, oxaliplatin and leucovorin can be administered concurrently in separate bags using a Y-connector). Shorter oxaliplatin administration schedules (eg, 1 mg/m$^2$ per minute) appear to be safe.[3] | Day 1 |
| Leucovorin$^\Delta$ | 400 mg/m$^2$ IV$^\diamond$ | Dilute with 250 mL D5W¶ and administer over two hours concurrent with oxaliplatin. | Day 1 |
| Fluorouracil (FU) | 400 mg/m$^2$ IV bolus | Slow IV push over five minutes (administer immediately after leucovorin). | Day 1 |
| FU | 2400 mg/m$^2$ IV | Dilute with 500 to 1000 mL D5W¶ and administer over 46 hours (begin immediately after FU IV bolus). To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL) or the total dose can be diluted in 100 to 150 mL NS.¶ | Day 1 |
| **Pretreatment considerations:** | | | |
| **Emesis risk** | ▪ MODERATE.<br>▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults. | | |
| **Prophylaxis for infusion reactions** | ▪ There is no standard premedication regimen.<br>▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy. | | |
| **Vesicant/irritant properties** | ▪ Oxaliplatin and FU are classified as irritants, but oxaliplatin can cause significant tissue damage; avoid extravasation. | | |

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| | ▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants. |
| **Infection prophylaxis** | ▪ Primary prophylaxis with G-CSF is not justified (estimated risk of febrile neutropenia <5%[2]).<br>▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation. |
| **Dose adjustment for baseline liver or kidney dysfunction** | ▪ A lower starting dose of oxaliplatin may be needed for severe kidney impairment.[4] A lower starting dose of FU may be needed for patients with liver impairment.[5]<br>▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with kidney impairment, conventional cytotoxic agents. |
| **Maneuvers to prevent acute neurotoxicity** | ▪ Counsel patients to avoid exposure to cold during and for approximately 72 hours after each infusion. Prolongation of the oxaliplatin infusion time from two to six hours may mitigate acute neurotoxicity.<br>▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy. |
| **Cardiac issues** | ▪ QT prolongation and ventricular arrhythmias have been reported after oxaliplatin. ECG monitoring is recommended if therapy is initiated in patients with heart failure, bradyarrhythmias, coadministration of drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid oxaliplatin in patients with congenital long QT syndrome. Correct hypokalemia and hypomagnesemia prior to initiating oxaliplatin. |

**Monitoring parameters:**

- CBC with differential and platelet count prior to each treatment.
- Assess electrolytes (especially potassium and magnesium) and liver and kidney function prior to each treatment.
- Assess changes in neurologic function prior to each treatment.

**Suggested dose modifications for toxicity:**

| | |
|---|---|
| **Myelotoxicity** | ▪ Delay treatment cycle by one week for ANC <1500/microL, or platelets <75,000/microL on the day of treatment. If treatment is delayed for two |

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| | weeks or delayed for one week on two separate occasions, eliminate FU bolus. With the second occurrence, reduce infusional FU by 20% and reduce oxaliplatin dose from 85 to 65 mg/m$^2$. |
| **Neurologic toxicity** | ▪ For grade 2 symptoms lasting longer than seven days, decrease oxaliplatin dose by 20%. Discontinue oxaliplatin for grade 3 paresthesias/dysesthesias. The US Prescribing Information recommends a dose reduction in oxaliplatin (to 75 mg/m$^2$ in patients treated in the adjuvant setting and to 65 mg/m$^2$ in patients with advanced disease) for persistent grade 2 neurosensory events that do not resolve and discontinuation for persistent grade 3 neurosensory events.[4]<br>▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[5] |
| **Diarrhea** | ▪ Withhold treatment for grade 2 or worse diarrhea, and restart at a 20% lower dose of all agents after complete resolution. The US Prescribing Information recommends dose reduction of oxaliplatin (to 75 mg/m$^2$ in patients treated in the adjuvant setting and to 65 mg/m$^2$ for patients treated for advanced disease), as well as a reduction of bolus FU and infusional FU after recovery from grade 3 or 4 diarrhea during the prior cycle.[4,5]<br>▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency.<br>▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents. |
| **Cardiopulmonary toxicity** | ▪ Oxaliplatin has rarely been associated with pulmonary toxicity. Withhold oxaliplatin for unexplained pulmonary symptoms until interstitial lung disease or pulmonary fibrosis is excluded.<br>▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents.<br>▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[5] |
| **If there is a change in body weight of at least 10%, doses should be recalculated.** | |

**This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.**

ANC: absolute neutrophil count; CBC: complete blood count; DPD: dihydropyrimidine dehydrogenase; D5W: 5% dextrose in water; ECG: electrocardiogram; G-CSF: granulocyte-colony stimulating factors; IV: intravenous; NS: normal saline; QT: time between the start of the Q wave and the end of the T wave (heart electrical cycle).

* Many centers routinely infuse oxaliplatin through a central venous line because of local pain with infusion into a peripheral vein.

¶ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

Δ Leucovorin dose is given for d,l-racemic mixture.[6] Use half the dose for LEVOleucovorin (l-leucovorin).

◇ The dose of leucovorin in the two trials of modified FOLFOX6 was 350 mg/$m^2$. However, most clinicians use the standard 400 mg/$m^2$ dose as was used for original FOLFOX6.[7]

*References:*

1. *Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer 2002; 87:393.*
2. *Hochster HS, Hart LL, Ramanathan RK, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. J Clin Oncol 2008; 26:3523.*
3. *Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: Oxaliplatin Can Be Safely Infused at a Rate of 1 mg/m2/min. J Oncol Pract 2016; 12:e459.*
4. *Oxaliplatin injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 13, 2015).*
5. *Fluorouracil injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 13, 2011).*
6. *Leucovorin calcium injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 13, 2011).*
7. *Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004; 22:229.*

Graphic 50132 Version 44.0

## Chemotherapy regimens for advanced esophagogastric cancer: Capecitabine plus oxaliplatin[1,2]

**Cycle length:** 21 days.
**Duration of therapy:** Treatment is continued until disease progression, unacceptable toxicity, or patient withdrawal.

| Drug | Dose and route | Administration | Given on days |
|---|---|---|---|
| Oxaliplatin | 130 mg/m$^2$ IV* | Dilute in 500 mL D5W¶ and administer over two hours. Shorter oxaliplatin administration schedules (eg, 1 mg/m$^2$ per minute) appear to be safe.[3] | Day 1 |
| Capecitabine$^{\Delta}$ | 850 mg/m$^2$ or 1000 mg/m$^2$ per dose, by mouth$^{\diamond}$ | Twice daily (total dose 1700 or 2000 mg/m$^2$ per day). Swallow whole with water within 30 minutes after a meal, with each dose as close to 12 hours apart as possible. Do not cut or crush tablets.§ | Days 1 to 14 |

**Pretreatment considerations:**

| | |
|---|---|
| **Emesis risk** | ▪ Oxaliplatin: MODERATE.<br>▪ Oral capecitabine: LOW.<br>▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults. |
| **Prophylaxis for infusion reactions** | ▪ There is no standard premedication regimen for oxaliplatin.<br>▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy. |
| **Vesicant/irritant properties** | ▪ Oxaliplatin is an irritant but can cause significant tissue damage; avoid extravasation.<br>▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants. |
| **Infection prophylaxis** | ▪ Primary prophylaxis with G-CSF is not indicated (estimated risk of febrile neutropenia is <5%).<br>▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and |

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| | hematopoietic cell transplantation. |
| **Dose adjustment for baseline liver or kidney dysfunction** | ▪ Lower starting doses of oxaliplatin and capecitabine may be needed for kidney impairment.<br>▪ Refer to UpToDate topics on chemotherapy nephrotoxicity and dose modification in patients with kidney insufficiency, conventional cytotoxic agents. |
| **Maneuvers to prevent neurotoxicity** | ▪ Counsel patients to avoid exposure to cold during and for approximately 48 hours after each infusion. Prolongation of the oxaliplatin infusion time from two to six hours may mitigate acute neurotoxicity.<br>▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy. |
| **Cardiac issues** | ▪ Prolongation of the corrected QT (QTc) interval and ventricular arrhythmias have been reported after oxaliplatin. ECG monitoring is recommended if therapy is initiated in patients with heart failure, bradyarrhythmias, coadministration of drugs known to prolong the QTc interval, and electrolyte abnormalities. Avoid oxaliplatin in patients with congenital long QT syndrome. Correct hypokalemia and hypomagnesemia prior to initiating oxaliplatin.<br>▪ Refer to UpToDate topics on cardiotoxicity of cancer chemotherapy agents other than anthracyclines, HER2-targeted agents, and fluoropyrimidines. |

**Monitoring parameters:**

- CBC with differential and platelet count weekly during treatment.
- Assess electrolytes (especially potassium and magnesium) and liver and kidney function every three weeks prior to each new cycle of treatment.
- Assess changes in neurologic function prior to each treatment.
- Monitor for diarrhea and palmar-plantar erythrodysesthesias during treatment.
- Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents and cutaneous side effects of conventional chemotherapy agents.
- More frequent anticoagulant response (INR or prothrombin time) monitoring is necessary for patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy.
- Cardiotoxicity observed with capecitabine includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. These adverse reactions may be more common in patients with a prior history of coronary artery disease.

- Refer to UpToDate topics on cardiotoxicity of non-anthracycline cancer chemotherapy agents.

| Suggested dose modifications for toxicity: | |
|---|---|
| **Myelotoxicity** | ▪ A new cycle of treatment should not start until neutrophils recover to >1500/microL and platelets recover to >100,000/microL.[2] Interrupt capecitabine until the next cycle begins for any grade 2 or worse hematologic toxicity and delay treatment until complete recovery or improvement to ≤grade 1. After recovery, reduce doses of both drugs by 20% for febrile neutropenia in the preceding cycle.[1] |
| **Gastrointestinal toxicity** | ▪ Interrupt capecitabine until the initiation of the next cycle and delay oxaliplatin for any grade 2 or worse gastrointestinal toxicity; restart treatment only after complete recovery or improvement to ≤grade 1. Reduce the capecitabine dose by 20% in subsequent cycles at the first occurrence of grade 2 gastrointestinal toxicity, and by 30% for grade 3 or 4 toxicity including mucositis.[1] After recovery, reduce the dose of oxaliplatin by 25% for grade 4 diarrhea.[1]<br>▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after capecitabine should prompt evaluation for DPD deficiency.<br>▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents. |
| **Neurotoxicity¥** | ▪ Reduce the dose of oxaliplatin by 25% for persistent (14 days or longer) paresthesia or temporary (7 to 14 days) painful paresthesia or functional impairment.[2] For persistent painful paresthesia or functional impairment omit oxaliplatin until recovery and restart at 50% of dose.[2] Discontinue if toxicities recur despite dose reduction. |
| **Pulmonary toxicity** | ▪ Oxaliplatin has rarely been associated with pulmonary toxicity. Withhold oxaliplatin for unexplained pulmonary symptoms until interstitial lung disease or pulmonary fibrosis is excluded.[1]<br>▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents. |
| **Other toxicity (including hepatotoxicity)** | ▪ Interrupt capecitabine and delay oxaliplatin for any grade 2 or worse non-neurologic toxicity (except alopecia); restart treatment only after complete recovery or improvement to ≤grade 1.[2] Patients with grade 3 or 4 hyperbilirubinemia may resume capecitabine once toxicity has reduced to grade ≤2, but at a reduced dose.[4]<br>▪ Reduce the dose of oxaliplatin by 25% for any drug-related grade 3 toxicity other than that described above. Reduce the capecitabine dose b 20 to 30% in subsequent cycles for grade 2 or grade 3 toxicity (including hand-foot syndrome) during a preceding cycle.[1] |

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|---|---|
| | ▪ Discontinue capecitabine permanently if, despite dose reduction, a given toxicity occurs for the fourth time at grade 2, third time at grade 3, or a second time at grade 4.[4]<br>▪ For transient kidney insufficiency in the preceding cycle, reduce doses of both drugs. |
| **Doses of capecitabine omitted for toxicity are not replaced or restored; instead the patient should resume with the next planned treatment cycle.** | |
| **If there is a change in body weight of at least 10%, doses should be recalculated.** | |

**This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.**

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CBC: complete blood count; DPD: dihydropyrimidine dehydrogenase; D5W: 5% dextrose in water; ECG: electrocardiogram; G-CSF: granulocyte colony stimulating factor; INR: international normalized ratio; IV: intravenous; QT: time between the start of the Q wave and the end of the T wave (heart electrical cycle).
* Many centers routinely infuse oxaliplatin through a central venous line because of local pain with infusion into a peripheral vein.

¶ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies). Oxaliplatin is incompatible with normal saline and a D5W flush is recommended prior to starting the drug infusion.

Δ No capecitabine dose has been shown to be safe in patients with complete DPD deficiency, and data are insufficient to recommend a dose in patients with partial DPD activity.

◇ The original protocol used 1000 mg/$m^2$ orally, twice daily, for 14 days. The United States Prescribing Information suggests 850 mg/$m^2$ or 1000 mg/$m^2$, twice daily, and that the dose be individualized based on patient risk factors and adverse reactions.

§ Extemporaneous compounding of liquid dosage forms has been recommended, but IV therapies may be more appropriate for patients with significant swallowing difficulty.

¥ Neurotoxicity was graded in the original study based on the Levis scale: Grade 1, paresthesias of moderate intensity lasting less than seven days; grade 2, painful paresthesias lasting 8 to 14 days (without functional impairment); grade 3, persistent (>14 days) paresthesias (without functional impairment); grade 4, beginning functional impairment.

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*References:*

1. *Jatoi A, Murphy BR, Foster NR, et al. Oxaliplatin and capecitabine in patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction and gastric cardia: A phase II study from the North Central Cancer Treatment Group. Ann Oncol 2006; 17:29.*
2. *van Meerten E, Eskens FA, van Gameren EC, et al. First-line treatment with oxaliplatin and capecitabine in patients*

*with advanced or metastatic oesophageal cancer: A phase II study. Br J Cancer 2007; 96:1348.*

3. *Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: Oxaliplatin can be safely infused at a rate of 1 mg/m2/min. J Oncol Pract 2016; 12:e459.*
4. *Capecitabine. United States Prescribing Information. US National Library of Medicine. (Available online at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020896s044s045s046s047s048s049s050s051lbl.pdf, accessed on December 20, 2022).*

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Graphic 112347 Version 13.0

## Cardiac ineligibility criteria in the NSABP B-31 and NCCTG N9831 adjuvant trastuzumab trials

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| Angina pectoris requiring antianginal medication |
| Arrhythmia requiring medication |
| Severe conduction abnormality |
| Clinically significant valvular heart disease |
| Cardiomegaly on chest radiography |
| Left ventricular hypertrophy on echocardiogram (NSABP B-31 only) |
| Poorly controlled hypertension |
| Clinically significant pericardial effusion (NCCTG trial N9831 only) |
| History of myocardial infarction, heart failure, or cardiomyopathy |
| Left ventricular ejection fraction below the lower limit of normal |

NSABP: National Surgical Adjuvant Breast and Bowel Project; NCCTG: North Central Cancer Treatment Group.

Graphic 74571 Version 2.0

## Response Evaluation Criteria in Solid Tumors (RECIST)

| Response assessment | RECIST guideline, version 1.0[1] | RECIST guideline, version 1.1[2] |
|---|---|---|
| **Target lesions** | | |
| CR | Disappearance of all target lesions | Disappearance of all target lesions and reduction in the short axis measurement of all pathologic lymph nodes to ≤10 mm |
| PR | ≥30% decrease in the sum of the longest diameter of the target lesions compared with baseline | ≥30% decrease in the sum of the longest diameter of the target lesions compared with baseline |
| PD | ≥20% increase in the sum of the longest diameter of the target lesions compared with the smallest sum of the longest diameter recorded since treatment started<br>**OR**<br>The appearance of 1 or more new lesions | ≥20% increase of at least 5 mm in the sum of the longest diameter of the target lesions compared with the smallest sum of the longest diameter recorded<br>**OR**<br>The appearance of new lesions, including those detected by FDG-PET |
| SD | Neither PR nor PD | Neither PR nor PD |
| **Non-target lesions** | | |
| CR | Disappearance of all non-target lesions and normalization of tumor marker levels | Disappearance of all non-target lesions and normalization of tumor marker levels |
| IR, SD | Persistence of 1 or more non-target lesions and/or the maintenance of tumor marker levels above normal limits | Persistence of 1 or more non-target lesions and/or the maintenance of tumor marker levels above normal limits |
| PD | Appearance of 1 or more new lesions and/or unequivocal progression of | The appearance of 1 or more new lesions or unequivocal progression<br>If patient has measurable disease, an increase in th |

| | | |
|---|---|---|
| | existing non-target lesions | overall level or substantial worsening in non-target lesions, such that tumor burden has increased, ever if there is SD or PR in target lesions<br><br>If no measurable disease, an increase in the overall tumor burden comparable in magnitude with the increase that would be required to declare PD in measurable disease (eg, an increase in pleural effusions from trace to large, or an increase in lymphangitic disease from localized to widespread) |

CR: complete response; PR: partial response; PD: progressive disease; FDG-PET: fludeoxyglucose positron emission tomography; SD: stable disease; IR: incomplete response.

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*References:*

1. *Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92:205.*
2. *Eisenhauer E, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228.*

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Graphic 74693 Version 13.0

## Chemotherapy regimens for HER2-overexpressing* metastatic gastric and gastroesophageal junction cancer: FOLFOX plus trastuzumab[1]

| **Cycle length:** 14 days. | | | |
|---|---|---|---|
| **Drug** | **Dose and route** | **Administration** | **Given on days** |
| Trastuzumab | 6 mg/kg IV (loading dose) | Dilute in 250 mL NS¶ and administer over 90 minutes for the loading dose. **Do not** mix with D5W and **do not** infuse as an IV push or bolus. | Day 1 (cycle 1 only) |
| Trastuzumab | 4 mg/kg IV | Dilute in 250 mL NS¶ and administer over 30 minutes. **Do not** mix with D5W and **do not** infuse as an IV push or bolus. | Day 1 of every subsequent cycle, starting with cycle 2 |
| Oxaliplatin$^{\Delta}$ | 85 mg/m$^2$ IV | Dilute with 500 mL D5W¶ and administer over two hours. Oxaliplatin and leucovorin can be administered concurrently in separate bags using a Y-connector. Shorter oxaliplatin administration schedules (eg, 1 mg/m$^2$ per minute) appear to be safe.[2] | Day 1 |
| Leucovorin$^{\diamond}$ | 400 mg/m$^2$ IV | Dilute with 250 mL D5W¶ and administer over two hours concurrent with oxaliplatin. | Day 1 |
| Fluorouracil (FU)§ | 400 mg/m$^2$ IV bolus | Slow IV push (over two to five minutes). Administer immediately after leucovorin. | Day 1 |
| FU | 2400 mg/m$^2$ total dose IV | Dilute with 500 to 1000 mL D5W¶ and administer as continuous IV over 46 hours (begin immediately after FU IV bolus). To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL) or the total dose can be diluted in 100 to 150 mL NS. | Day 1 |

| Pretreatment considerations: | |
|---|---|
| **Emesis risk** | ▪ MODERATE.<br>▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults. |
| **Prophylaxis for infusion reactions** | ▪ There is no standard premedication regimen for FOLFOX. Most clinicians do not routinely premedicate prior to the first trastuzumab dose. However, patients may be instructed to self-administer acetaminophen or an NSAID if flu-like symptoms develop within 24 hours of drug administration.<br>▪ Refer to UpToDate topics on infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy and infusion reactions to systemic chemotherapy. |
| **Vesicant/irritant properties** | ▪ Oxaliplatin and FU are classified as irritants, but oxaliplatin (rare) can cause significant tissue damage; avoid extravasation.<br>▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants. |
| **Infection prophylaxis** | ▪ Primary prophylaxis with G-CSF is not justified (estimated risk of febrile neutropenia <5%[1]).<br>▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation. |
| **Dose adjustment for baseline liver or kidney dysfunction** | ▪ A lower starting dose of oxaliplatin may be needed for severe kidney impairment.[3] A lower starting dose of FU may be needed for patients with liver impairment.<br>▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with kidney insufficiency, conventional cytotoxic agents. |
| **Maneuvers to prevent neurotoxicity** | ▪ Counsel patients to avoid exposure to cold during and for approximately 72 hours after each infusion. Prolongation of the oxaliplatin infusion time from two to six hours may mitigate acute neurotoxicity.<br>▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy. |
| **Cardiopulmonary** | ▪ Prolongation of the corrected QT interval (QTc) and ventricular |

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|---|---|
| **issues** | arrhythmias has been reported after oxaliplatin. ECG monitoring is recommended if therapy is initiated in patients with heart failure, bradyarrhythmias, coadministration of drugs known to prolong the QTc interval, and electrolyte abnormalities. Avoid oxaliplatin in patients with congenital long QT syndrome. Correct hypokalemia and hypomagnesemia prior to initiating oxaliplatin. Cases of pulmonary fibrosis are rarely reported with oxaliplatin.<br>▪ Trastuzumab is associated with cardiotoxicity; assess baseline LVEF prior to therapy and then at least every three months during therapy.[4] Patients with heart failure or a baseline LVEF <50% were excluded from the study.[1] Trastuzumab may cause serious pulmonary toxicity and should be used with caution in patients with preexisting pulmonary disease.<br>▪ Refer to UpToDate topics on cardiotoxicity of trastuzumab and other HER2-targeted agents.<br>▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy.<br>▪ Refer to UpToDate topics on cardiotoxicity of cancer chemotherapy agents other than anthracyclines, HER2-targeted agents, and fluoropyrimidines. |

**Monitoring parameters:**

- CBC with differential and platelet count prior to each treatment.
- Assess electrolytes (especially potassium and magnesium) and liver and kidney function every two weeks prior to each treatment.
- Assess changes in neurologic function prior to each treatment.
- Monitor for infusion reactions, especially during the first two courses of trastuzumab.
- Monitor for mucositis, diarrhea, and palmar-plantar erythrodysesthesias during treatment.
- Refer to UpToDate topics on oral toxicity associated with chemotherapy, cutaneous side effects of conventional chemotherapy agents, and enterotoxicity of chemotherapeutic agents.
- Assess cardiac function as clinically indicated.
- Refer to UpToDate topics on cardiotoxicity of trastuzumab and other HER2-targeted agents.

**Suggested dose modifications for toxicity:**

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|---|---|
| **Myelotoxicity** | ▪ Delay treatment cycle by one week for absolute neutrophil count <1500/microL or platelets <75,000/microL on the day of treatment. If treatment is delayed for two weeks or delayed for one week on two |

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|---|---|
| | separate occasions, eliminate FU bolus. With the second occurrence, reduce infusional FU by 20% and reduce oxaliplatin dose from 85 to 65 mg/m$^2$.[3]<br>▪ **NOTE:** Severe myelosuppression after FU should prompt evaluation for DPD deficiency. |
| **Neurologic toxicity** | ▪ Withhold oxaliplatin for persisting grade 2 or any grade 3 paresthesias/dysesthesias until recovery.[1] The United States Prescribing Information recommends a dose reduction in oxaliplatin to 65 mg/m$^2$ for persistent grade 2 neurosensory events that do not resolve, and permanent discontinuation for persistent grade 3 neurosensory events.[3]<br>▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy.<br>▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[5] |
| **Gastrointestinal toxicity** | ▪ Withhold treatment for grade 2 or worse diarrhea, and restart at a 20% lower dose of all agents after complete resolution. The United States Prescribing Information recommends dose reduction of oxaliplatin to 65 mg/m$^2$ as well as a reduction of bolus FU and infusional FU after recovery from grade 3 or 4 diarrhea during the prior cycle.[3]<br>▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency.[5]<br>▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents. |
| **Cardiotoxicity** | ▪ Assess LVEF at least every three months during trastuzumab.[4] The United States Prescribing Information recommends withholding trastuzumab for at least four weeks for LVEF ≥16% decrease from baseline or LVEF below normal limits and ≥10% decrease from baseline; repeat LVEF assessment every four weeks. May resume trastuzumab treatment if LVEF returns to normal limits within four to eight weeks and remains at ≤15% decrease from baseline value. Discontinue permanently for persistent (>8 weeks) LVEF decline or for >3 incidents of treatment interruptions for cardiomyopathy.[4] Guidelines for managing cardiac dysfunction during therapy with HER2-targeted agents are available.<br>▪ Refer to UpToDate topics on cardiotoxicity of trastuzumab and other HER2-targeted agents.<br>▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG |

| | |
|---|---|
| | changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[5] |
| **Pulmonary toxicity** | ▪ Discontinue trastuzumab for serious pulmonary toxicity. Withhold oxaliplatin for unexplained pulmonary symptoms until interstitial lung disease or pulmonary fibrosis is excluded.<br>▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, molecularly targeted agents and pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents. |
| **If there is a change in body weight of at least 10%, doses should be recalculated.** | |

**This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.**

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CBC: complete blood count; DPD: dihydropyrimidine dehydrogenase; D5W: 5% dextrose in water; ECG: electrocardiogram; FISH: fluorescence in situ hybridization; G-CSF: granulocyte-colony stimulating factors; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemical; IV: intravenous; LVEF: left ventricular ejection fraction; NS: normal saline; NSAID: nonsteroidal anti-inflammatory drug; QT: time between the start of the Q wave and the end of the T wave (heart electrical cycle).

* High levels of HER2 overexpression, as determined by either 3+ IHC staining or positive FISH, are used to select patients for therapy with trastuzumab. Refer to UpToDate topics on initial systemic therapy for locally advanced unresectable and metastatic esophageal and gastric cancer.

¶ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

Δ Many centers routinely infuse oxaliplatin through a central venous catheter because of local pain with infusion into a peripheral vein.

◇ Leucovorin dose is given for dl-racemic mixture.[6] Use half the dose for LEVOleucovorin (l-leucovorin).

§ No FU dose has been shown to be safe in patients with complete DPD deficiency, and data are insufficient to recommend a dose in patients with partial DPD activity.

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*References:*

1. *Soularue E, Cohen R, Tournigand C, et al. 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 2015; 102:324.*
2. *Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: Oxaliplatin can be safely infused at a rate of 1 mg/m2/min. J Oncol*

*Pract 2016; 12:e459.*

3. *Oxaliplatin injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on May 11, 2016).*
4. *Trastuzumab injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on May 11, 2016).*
5. *Fluorouracil injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on May 11, 2016).*
6. *Leucovorin calcium injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on May 11, 2016).*

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Graphic 109416 Version 12.0

## Chemotherapy regimens for HER2-overexpressing* advanced gastric and gastroesophageal junction cancer: Capecitabine and oxaliplatin (CAPOX) plus trastuzumab[1]

**Cycle length:** 21 days.

| Drug | Dose and route | Administration | Given on days |
|---|---|---|---|
| Trastuzumab | Loading dose: 8 mg/kg IV | Dilute in 250 mL NS¶ and administer over 90 minutes for the loading dose. **Do not** mix with D5W and **do not** infuse as an IV push or bolus. | Day 1 (cycle 1) |
| Trastuzumab | 6 mg/kg IV | Dilute in 250 mL NS¶ and administer over 30 to 90 minutes. **Do not** mix with D5W and **do not** infuse as an IV push or bolus. | Day 1 of every subsequent cycle, starting with cycle 2 |
| Oxaliplatin$^{\Delta}$ | 130 mg/m$^2$ IV | Dilute in 500 mL D5W¶ and administer over two hours. Shorter oxaliplatin administration schedules (eg, 1 mg/m$^2$ per minute) appear to be safe.[2] | Day 1 |
| Capecitabine$^{\diamond}$ | 1000 mg/m$^2$ orally per dose | Twice daily (total dose 2000 mg/m$^2$ per day); swallow whole with water within 30 minutes after a meal, with each dose as close to 12 hours apart as possible. Do not cut or crush tablets.§ | Days 1 to 14 |

**Pretreatment considerations:**

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| **Emesis risk** | ▪ Oxaliplatin: MODERATE.<br>▪ Oral capecitabine: LOW.<br>▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults. |
| **Prophylaxis for infusion reactions** | ▪ There is no standard premedication regimen for oxaliplatin. Most clinicians do not routinely premedicate prior to the first trastuzumab dose. However, patients may be instructed to self-administer acetaminophen or an NSAID if flu-like symptoms develop within 24 hours of drug administration.<br>▪ Refer to UpToDate topics on infusion-related reactions to therapeutic |

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| | monoclonal antibodies used for cancer therapy and infusion reactions to systemic chemotherapy. |
| **Vesicant/irritant properties** | ▪ Oxaliplatin is classified as an irritant, but can cause significant tissue damage (rare); avoid extravasation.<br>▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants. |
| **Infection prophylaxis** | ▪ Primary prophylaxis with G-CSF is not justified (estimated risk of febrile neutropenia <20%[1]).<br>▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation. |
| **Dose adjustment for baseline liver or kidney dysfunction** | ▪ Lower starting doses of oxaliplatin and capecitabine may be needed for kidney impairment.<br>▪ Refer to UpToDate topics on chemotherapy nephrotoxicity and dose modification in patients with kidney insufficiency, conventional cytotoxic agents. |
| **Maneuvers to prevent neurotoxicity** | ▪ Counsel patients to avoid exposure to cold during and for approximately 72 hours after each infusion. Prolongation of the oxaliplatin infusion time from two to six hours may mitigate acute neurotoxicity.<br>▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy. |
| **Cardiac issues** | ▪ Prolongation of the corrected QT (QTc) interval and ventricular arrhythmias have been reported after oxaliplatin. ECG monitoring is recommended if therapy is initiated in patients with heart failure, bradyarrhythmias, coadministration of drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid oxaliplatin in patients with congenital long QT syndrome. Correct hypokalemia and hypomagnesemia prior to initiating oxaliplatin. Pulmonary toxicity is rarely reported with oxaliplatin.<br>▪ Trastuzumab is associated with cardiomyopathy; assess baseline LVEF prior to therapy and at least every three months during therapy.[3] Patients with heart failure, coronary artery disease, myocardial infarction in the prior six months, or baseline LVEF <50% were excluded from the study.[1] Trastuzumab may also cause serious pulmonary toxicity and should be used with caution in patients with preexisting pulmonary disease.<br>▪ Refer to UpToDate topics on cardiotoxicity of cancer chemotherapy agents other than anthracyclines, HER2-targeted agents, and |

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| | fluoropyrimidines and cardiotoxicity of trastuzumab and other HER2-targeted agents. |

**Monitoring parameters:**

- Obtain CBC with differential and platelet count prior to each treatment.
- Assess electrolytes and liver and kidney function every three weeks prior to each new treatment.
- Assess changes in neurologic function prior to each treatment.
- Assess cardiac function every three months during therapy or as clinically indicated.
- Monitor for mucositis, diarrhea, and palmar-plantar erythrodysesthesias during treatment.
- Refer to UpToDate topics on oral toxicity associated with chemotherapy, cutaneous side effects of conventional chemotherapy agents, and enterotoxicity of chemotherapeutic agents.
- More frequent anticoagulant response (INR or prothrombin time) monitoring is necessary for patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy.
- Cardiotoxicity observed with capecitabine includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy.
- Refer to UpToDate topics on cardiotoxicity of non-anthracycline cancer chemotherapy agents.

**Suggested dose modifications for toxicity:**

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| **Myelotoxicity** | ▪ A new cycle of treatment should not start until neutrophils recover to >1500/microL and platelets recover to >100,000/microL. Interrupt capecitabine for any grade 2 or worse hematologic toxicity and delay treatment with both capecitabine and oxaliplatin until complete recovery or improvement to ≤grade 1.[4] Reduce the capecitabine dose by 25% in subsequent cycles at the first occurrence of a grade 2 or grade 3 toxicity, and by 50% at the second occurrence of a given grade 2 or grade 3 toxicity or at the first occurrence of a grade 4 event. After recovery, reduce oxaliplatin by 25% for any intracycle grade 3 or 4 neutropenia or thrombocytopenia. Discontinue capecitabine and oxaliplatin permanently if, despite dose reduction, hematologic toxicity occurs for the third time at grade 2 or grade 3, or a second time at grade 4. |
| **Neurotoxicity** | ▪ Withhold oxaliplatin for persisting grade 2 or any grade 3 paresthesias/dysesthesias until recovery.[1] The United States Prescribing Information recommends a dose reduction in oxaliplatin to 65 mg/m$^2$ for persistent grade 2 neurosensory events that do not resolve, and |

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| | permanent discontinuation for persistent grade 3 neurosensory events.[5]<br>▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy. |
| **Gastrointestinal toxicity** | ▪ Interrupt capecitabine and delay oxaliplatin for any grade 2 or worse gastrointestinal toxicity; restart treatment only after complete recovery o improvement to ≤grade 1.[4,6] After recovery, reduce the dose of oxaliplatin by 25% after the first episode of grade 3 or worse diarrhea or mucositis. Reduce the capecitabine dose by 25% in subsequent cycles at the first occurrence of grade 2 or 3 toxicity, and by 50% at the second occurrence of a given grade 2 or grade 3 toxicity or at the first occurrence of a grade 4 event. Discontinue capecitabine permanently if, despite dose reduction, a given toxicity occurs for the third time at grade 2 or grade 3, or a second time at grade 4.[4]<br>▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after capecitabine should prompt evaluation for dihydropyrimidine dehydrogenase deficiency.<br>▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents. |
| **Cardiotoxicity** | ▪ Assess LVEF at least every three months during trastuzumab.[3] In the original trial, if LVEF decreased by 10 points from baseline and to below 50%, trastuzumab was withheld and a repeat LVEF assessment performed within three weeks.[1] If LVEF failed to improve, discontinuation of trastuzumab was suggested. The United States Prescribing Information suggests withholding trastuzumab for at least four weeks for LVEF ≥16% decrease from baseline or LVEF below normal limits and ≥10% decrease from baseline, and repeat LVEF every four weeks. May resume trastuzumab treatment if LVEF returns to normal limits within four to eight weeks and remains at ≤15% decrease from baseline value. Discontinue permanently for persistent (>8 weeks) LVEF decline or for >3 incidents of treatment interruptions for cardiomyopathy[3] Guidelines for managing cardiac dysfunction during therapy with HER2-targeted agents are available.<br>▪ Refer to UpToDate topics on cardiotoxicity of trastuzumab and other HER2-targeted agents. |
| **Pulmonary toxicity** | ▪ Discontinue trastuzumab for serious pulmonary toxicity. Withhold oxaliplatin for unexplained pulmonary symptoms until interstitial lung disease or pulmonary fibrosis is excluded.<br>▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, molecularly targeted agents and pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents. |

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| **Other toxicities (including hepatotoxicity)** | ▪ Interrupt capecitabine and delay oxaliplatin for any grade 2 or worse other non-neurologic toxicity (except alopecia); restart treatment only after complete recovery or improvement to ≤grade 1.[4]<br>▪ Patients with grade 3 or 4 hyperbilirubinemia may resume capecitabine once toxicity has reduced to grade ≤2, but at a reduced dose.[4]<br>▪ Reduce the dose of oxaliplatin for subsequent cycles by 25% for drug-related grade 3 toxicity. Reduce the capecitabine dose by 25% in subsequent cycles at the first occurrence of a grade 2 or grade 3 toxicity, and by 50% at the second occurrence of a given grade 2 or grade 3 toxicity or at the first occurrence of a grade 4 event.<br>▪ Discontinue capecitabine permanently if, despite dose reduction, a given toxicity occurs for the third time at grade 2 or grade 3, or a second time at grade 4.[4] |
| **Doses of capecitabine omitted for toxicity are not replaced or restored; instead the patient should resume with the next planned treatment cycle.** | |
| **If there is a change in body weight of at least 10%, doses should be recalculated.** | |

**This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.**

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CBC: complete blood count; DPD: dihydropyrimidine dehydrogenase; D5W: 5% dextrose in water; ECG: electrocardiogram; FISH: fluorescence in situ hybridization; G-CSF: granulocyte-colony stimulating factors; HER2: human epidermal growth factor 2 receptor; IHC: immunohistochemical; INR: international normalized ratio; IV: intravenous; LVEF: left ventricular ejection fraction; NS: normal saline; NSAID: nonsteroidal anti-inflammatory drug; QT: time between the start of the Q wave and the end of the T wave (heart electrical cycle).

* High levels of HER2 overexpression, as determined by either 3+ IHC staining or positive FISH, are used to select patients for therapy with trastuzumab. Refer to UpToDate topics on initial systemic therapy for locally advanced unresectable and metastatic esophageal and gastric cancer.

¶ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

Δ Many centers routinely infuse oxaliplatin through a central venous catheter because of local pain with infusion into a peripheral vein.

◇ No capecitabine dose has been shown to be safe in patients with complete DPD deficiency, and data are insufficient to recommend a dose in patients with partial DPD activity.

§ Extemporaneous compounding of liquid dosage forms has been reported,[7] but intravenous alternatives may be more appropriate for patients with significant swallowing difficulty.

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*References:*

1. *Gong J, Liu T, Fan Q, et al. Optimal regimen of trastuzumab in combination with oxaliplatin/capecitabine in first-line treatment of HER2-positive advanced gastric cancer (CGOG1001): A multicenter, phase II trial. BMC Cancer 2016; 16:68.*
2. *Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: Oxaliplatin can be safely infused at a rate of 1 mg/m2/min. J Oncol Pract 2016; 12:e459.*
3. *Trastuzumab injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on May 11, 2016).*
4. *Nehls O, Oettle H, Hartmann JT, et al. Capecitabine plus oxaliplatin as first-line treatment in patients with advanced biliary system adenocarcinoma: A prospective multicentre phase II trial. Br J Cancer 2008; 98:309.*
5. *Oxaliplatin injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on May 11, 2016).*
6. *Capecitabine. United States Prescribing Information. US National Library of Medicine. (Available online at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020896s044s045s046s047s048s049s050s051lbl.pdf, accessed on December 20, 2022).*
7. *Lam MS. Extemporaneous compounding of oral liquid dosage formulations and alternative drug delivery methods for anticancer drugs. Pharmacotherapy 2011; 31:164.*

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Graphic 109415 Version 16.0

## Systemic therapy regimens for HER2-overexpressing* metastatic gastric and gastroesophageal junction cancer: Pembrolizumab plus FOLFOX and trastuzumab[1,2]

**Cycle length:** 14 days.

| Drug | Dose and route | Administration | Given on days |
|---|---|---|---|
| Trastuzumab | 6 mg/kg IV (loading dose) | Dilute in 250 mL NS¶ and administer over 90 minutes for the loading dose. **Do not** mix with D5W and **do not** infuse as an IV push or bolus. | Day 1 (cycle 1 only) |
| Trastuzumab | 4 mg/kg IV | Dilute in 250 mL NS¶ and administer over 30 minutes. **Do not** mix with D5W and **do not** infuse as an IV push or bolus. | Day 1 of every subsequent cycle, starting with cycle 2 |
| Oxaliplatin$^{\Delta}$ | 85 mg/m$^2$ IV | Dilute with 500 mL D5W¶ and administer over two hours. Oxaliplatin and leucovorin can be administered concurrently in separate bags using a Y-connector. Shorter oxaliplatin administration schedules (eg, 1 mg/m$^2$ per minute) appear to be safe.[3] | Day 1 |
| Leucovorin$^{\diamond}$ | 400 mg/m$^2$ IV | Dilute with 250 mL D5W¶ and administer over two hours concurrent with oxaliplatin. | Day 1 |
| Fluorouracil (FU)$^{\S\,¥}$ | 400 mg/m$^2$ IV bolus | Slow IV push (over two to five minutes). Administer immediately after leucovorin. | Day 1 |
| FU | 2400 mg/m$^2$ total dose IV | Dilute with 500 to 1000 mL D5W¶ and administer as continuous IV over 46 hours (begin immediately after FU IV bolus). To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL) or the total dose can be diluted in 100 to 150 | Day 1 |

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| | | mL NS. | |
| Pembrolizumab | 200 mg IV | Dilute in NS or D5W[¶] to a final concentration between 1 and 10 mg/mL and infuse over 30 minutes through an 0.2- to 5-micron sterile, nonpyrogenic, low-protein-binding inline or add-on filter. | Day 1, every 3 weeks |
| **OR** | | | |
| Pembrolizumab | 400 mg IV | Dilute in NS or D5W[¶] to a final concentration between 1 and 10 mg/mL and infuse over 30 minutes through an 0.2- to 5-micron sterile, nonpyrogenic, low-protein-binding inline or add-on filter. | Day 1, every 6 weeks |

## Pretreatment considerations:

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| **Immune status** | ▪ Anti-PD-1 monoclonal antibodies generate an immune response that may aggravate underlying autoimmune disorders or prior immune-related adverse events. There are only limited data on the safety and efficacy of checkpoint inhibitors such as pembrolizumab in patients with an underlying autoimmune disorder. Pembrolizumab should be used with extreme caution in such individuals.[4] |
| **Emesis risk** | ▪ Oxaliplatin: MODERATE.<br>▪ Fluorouracil: LOW.<br>▪ Pembrolizumab and trastuzumab: LOW TO MINIMAL.<br>▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults. |
| **Prophylaxis for infusion reactions** | ▪ There is no standard premedication regimen for FOLFOX or pembrolizumab. Most clinicians do not routinely premedicate prior to the first trastuzumab dose. However, patients may be instructed to self-administer acetaminophen or an NSAID if flu-like symptoms develop within 24 hours of drug administration.<br>▪ Refer to UpToDate topics on infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy and infusion reactions to systemic chemotherapy. |
| **Vesicant/irritant properties** | ▪ Oxaliplatin and FU are classified as irritants, but oxaliplatin can cause significant tissue damage in rare cases; avoid extravasation.<br>▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants. |

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| **Infection prophylaxis** | ▪ Primary prophylaxis with G-CSF is not justified (estimated risk of febrile neutropenia <5%).[1]<br>▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation. |
| **Dose adjustment for baseline liver or kidney dysfunction** | ▪ A lower starting dose of oxaliplatin may be needed for severe kidney impairment.[5] A lower starting dose of FU may be needed for patients with liver impairment.<br>▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease and chemotherapy nephrotoxicity and dose modification in patients with kidney impairment, conventional cytotoxic agents. |
| **Thyroid function tests** | ▪ Assess baseline thyroid function tests (TSH, FT4) prior to initiation of therapy and periodically during treatment. |
| **Maneuvers to prevent neurotoxicity** | ▪ Counsel patients to avoid exposure to cold during and for approximately 72 hours after each infusion of oxaliplatin. Prolongation of the oxaliplatin infusion time from two to six hours may mitigate acute neurotoxicity.<br>▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy. |
| **Cardiopulmonary issues** | ▪ Prolongation of the QTc interval and ventricular arrhythmias has been reported after oxaliplatin. ECG monitoring is recommended if therapy is initiated in patients with heart failure, bradyarrhythmias, coadministration of drugs known to prolong the QTc interval, and electrolyte abnormalities. Avoid oxaliplatin in patients with congenital long QT syndrome. Correct hypokalemia and hypomagnesemia prior to initiating oxaliplatin. Cases of pulmonary fibrosis are rarely reported with oxaliplatin.<br>▪ Trastuzumab is associated with cardiotoxicity; assess baseline LVEF prior to therapy and then at least every three months during therapy.[6] Patients with heart failure or a baseline LVEF <50% were excluded from one study.[2] Trastuzumab may cause serious pulmonary toxicity and should be used with caution in patients with pre-existing pulmonary disease.<br>▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy.<br>▪ Refer to UpToDate topics on cardiotoxicity of trastuzumab and other |

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|---|---|
| | HER2-targeted agents and fluoropyrimidine-associated cardiotoxicity. |
| **Regulatory issues** | ▪ An FDA-approved patient medication guide, which is available with the United States Prescribing Information,[4] must be dispensed with pembrolizumab. |

## Monitoring parameters:

- CBC with differential and platelet count prior to each treatment.
- Assess electrolytes and liver and kidney function every two weeks prior to each treatment.
- Assess changes in neurologic function prior to each treatment.
- All patients should be closely monitored and evaluated for immune-mediated adverse effects at least every three weeks during therapy.
- Monitor for fatigue, colitis, hepatotoxicity, hypophysitis, adrenal insufficiency, hypo- or hyperthyroidism, nephrotoxicity, pneumonitis, hyperglycemia, and skin rash. Many other clinically relevant immune-mediated toxicities have been observed, which may involve any organ system or tissue, and may be severe or fatal.
- While immune-mediated toxicities generally occur during treatment with pembrolizumab, adverse reactions, including infusion-related reactions, may also develop weeks to months after therapy discontinuation.
- Refer to UpToDate topics on toxicities associated with checkpoint inhibitor immunotherapy.
- Assess cardiac function every three months during therapy or as clinically indicated.
- Refer to UpToDate topics on cardiotoxicity of trastuzumab and other HER2-targeted agents and fluoropyrimidine-associated cardiotoxicity.
- Monitor for infusion reactions during pembrolizumab infusion and during trastuzumab infusion. For pembrolizumab, interrupt infusion and permanently discontinue for severe or life-threatening infusion-related reactions, as indicated in the United States Prescribing Information.[7]
- Monitor for mucositis, diarrhea, and palmar-plantar erythrodysesthesia during treatment.
- Refer to UpToDate topics on oral toxicity associated with chemotherapy, cutaneous side effects of conventional chemotherapy agents, and enterotoxicity of chemotherapeutic agents.

## Suggested dose modifications for toxicity:

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| **Immune-mediated toxicity** | ▪ No dosage reductions of pembrolizumab are recommended; treatment is withheld or discontinued to manage toxicities.[2,7]<br>▪ In general, if an immune-mediated adverse event is suspected, evaluate appropriately to confirm or exclude other causes. Based on the type and severity of the reaction, withhold treatment and administer systemic glucocorticoids. Upon resolution to ≤grade 1, initiate glucocorticoid |

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| | taper. Immune-mediated adverse reactions that do not resolve with systemic glucocorticoids may be managed with other systemic immunosuppressants (based on limited data). Discontinue pembrolizumab permanently for any grade 4 or recurrent grade 3 immune-mediated adverse event or one that is life threatening, grade 3 pneumonitis, AST/ALT elevation >8 times ULN, total bilirubin elevation >3 times ULN in patients with no hepatic tumor involvement, AST/ALT elevation to >10 times ULN for hepatitis with hepatic tumor involvement grade ≥2 myocarditis, grade 3 neurologic toxicity, suspected exfoliative dermatologic condition, severe (grade 3) or life-threatening (grade 4) infusion reactions, or if there is an inability to reduce glucocorticoid dose to 10 mg or less of prednisone equivalent per day within 12 weeks of initiating glucocorticoids.[4]<br>▪ Guidelines for managing specific toxicities, including immune-mediated adverse events, are available in the United States Prescribing Information for pembrolizumab,[4] from ASCO,[7] from the MASCC,[8] from the NCCN,[9] and from the SITC.[10]<br>▪ Refer to UpToDate topics on toxicities associated with checkpoint inhibitor immunotherapy. |
| **Myelotoxicity** | ▪ Delay treatment cycle by one week for absolute neutrophil count <1500/microL or platelets <75,000/microL on the day of treatment. If treatment is delayed for two weeks or delayed for one week on two separate occasions, eliminate FU bolus. With the second occurrence, reduce infusional FU by 20% and reduce oxaliplatin dose from 85 to 65 mg/m$^2$.[5]<br>▪ **NOTE:** Severe myelosuppression after FU should prompt evaluation for DPD deficiency. |
| **Neurologic toxicity** | ▪ Withhold oxaliplatin for persisting grade 2 or any grade 3 paresthesias/dysesthesias until recovery.[1] The United States Prescribing Information recommends a dose reduction in oxaliplatin to 65 mg/m$^2$ for persistent grade 2 neurosensory events that do not resolve, and permanent discontinuation for persistent grade 3 neurosensory events.[5]<br>▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy.<br>▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[11] |
| **Gastrointestinal** | ▪ Withhold treatment for grade 2 or worse diarrhea, and restart at a 20% |

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| **toxicity** | lower dose of all agents after complete resolution. The United States Prescribing Information recommends dose reduction of oxaliplatin to 65 mg/m$^2$ as well as a reduction of bolus FU and infusional FU after recovery from grade 3 or 4 diarrhea during the prior cycle.[5]<br>▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency.[11]<br>▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents. |
| **Cardiotoxicity** | ▪ The United States Prescribing Information recommends withholding trastuzumab for at least four weeks for LVEF ≥16% decrease from baseline or LVEF below normal limits and ≥10% decrease from baseline; repeat LVEF assessment every four weeks.[6] May resume trastuzumab treatment if LVEF returns to normal limits within four to eight weeks and remains at ≤15% decrease from baseline value. Discontinue permanently for persistent (>8 weeks) LVEF decline or for >3 incidents of treatment interruptions for cardiomyopathy.[6] Guidelines for managing cardiac dysfunction during therapy with HER2-targeted agents are available.<br>▪ There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[11]<br>▪ Refer to UpToDate topics on cardiotoxicity of trastuzumab and other HER2-targeted agents and fluoropyrimidine-associated cardiotoxicity. |
| **Pulmonary toxicity** | ▪ Discontinue trastuzumab for serious pulmonary toxicity. Withhold oxaliplatin for unexplained pulmonary symptoms until interstitial lung disease or pulmonary fibrosis is excluded.<br>▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, molecularly targeted agents and pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents. |
| **If there is a change in body weight of at least 10%, doses should be recalculated.** | |

**This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of systemic therapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.**

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HER2: human epidermal growth factor receptor 2; IV: intravenous; NS: normal saline; D5W: 5% dextrose in water; PD-1: programmed cell death protein; NSAID: nonsteroidal anti-inflammatory drug; G-CSF: granulocyte-colony stimulating factors; TSH: thyroid-stimulating hormone; FT4: free thyroxine; QT: time between the start of the Q wave and the end of the T wave (heart electrical cycle); QTc: corrected QT; ECG: electrocardiogram; LVEF: left ventricular ejection fraction; FDA: US

Food and Drug Administration; CBC: complete blood count; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ULN: upper limit normal; ASCO: American Society of Clinical Oncology; MASCC: Multinational Association of Supportive Care in Cancer; NCCN: National Comprehensive Cancer Network; SITC: Society for Immunotherapy of Cancer; DPD: dihydropyrimidine dehydrogenase; IHC: immunohistochemical; FISH: fluorescence in situ hybridization.

* High levels of HER2 overexpression, as determined by either 3+ IHC staining or positive FISH, are used to select patients for therapy with trastuzumab. Refer to UpToDate topics on initial systemic therapy for locally advanced unresectable and metastatic esophageal and gastric cancer.

¶ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

Δ Many centers routinely infuse oxaliplatin through a central venous catheter because of local pain with infusion into a peripheral vein.

◇ Leucovorin dose is given for dl-racemic mixture.[12] Use half the dose for LEVOleucovorin (l-leucovorin).

§ No FU dose has been shown to be safe in patients with complete DPD deficiency, and data are insufficient to recommend a dose in patients with partial DPD activity.

¥ Some UpToDate experts omit the FU bolus for patients with metastatic disease.

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*References:*


1. *Soularue E, Cohen R, Tournigand C, et al. 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 2015; 102:324.*
2. *Janjigian Y, Kawazoe A, Yañez P, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. Nature 2021; 600:727.*
3. *Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: Oxaliplatin can be safely infused at a rate of 1 mg/m2/min. J Oncol Pract 2016; 12:e548.*
4. *Pembrolizumab. United States Prescribing Information. US National Library of Medicine. (Available at dailymed.nlm.nih.gov, accessed on December 14, 2022).*
5. *Oxaliplatin injection. United States Prescribing Information. US National Library of Medicine. (Available at dailymed.nlm.nih.gov, accessed on December 14, 2022).*
6. *Trastuzumab injection. United States Prescribing Information. US National Library of Medicine. (Available at dailymed.nlm.nih.gov, accessed on December 14, 2022).*
7. *Schneider BJ, Naidoo J, Santomasso BD, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol 2021; 39:4073.*
8. *MASCC 2020 clinical practice recommendations for the management of immune-mediated adverse events from checkpoint inhibitors. (Available at link.springer.com/journal/520/topicalCollection, accessed on April 18, 2023).*
9. *NCCN guidelines for management of immunotherapy-related toxicities. (Available at nccn.org, accessed on April 18, 2023).*
10. *SITC cancer immunotherapy guidelines. (Available at sitcancer.org/research/cancer-immunotherapy-guidelines, accessed on April 18, 2023).*
11. *Fluorouracil injection. United States Prescribing Information. US National Library of Medicine. (Available at dailymed.nlm.nih.gov, accessed on December 14, 2022).*
12. *Leucovorin calcium injection. United States Prescribing Information. US National Library of Medicine. (Available at dailymed.nlm.nih.gov, accessed on December 14, 2022).*

Graphic 141603 Version 1.0

## Systemic therapy regimens for advanced HER2-overexpressing* gastric and gastroesophageal junction adenocarcinoma: Pembrolizumab plus CAPOX (capecitabine and oxaliplatin) and trastuzumab[1]

**Cycle length:** 21 days.
**Duration of therapy:** Maximum 35 cycles or until disease progression.

| Drug | Dose and route | Administration | Given on days |
|---|---|---|---|
| Trastuzumab | Loading dose: 8 mg/kg IV | Dilute in 250 mL NS¶ and administer over 90 minutes for the loading dose. **Do not** mix with D5W and **do not** infuse as an IV push or bolus. | Day 1 (cycle 1 only) |
| Trastuzumab | 6 mg/kg IV | Dilute in 250 mL NS¶ and administer over 30 to 90 minutes. **Do not** mix with D5W and **do not** infuse as an IV push or bolus. | Day 1 of every subsequent cycle, starting with cycle 2 |
| Oxaliplatin$^{\Delta}$ | 130 mg/m$^2$ IV | Dilute in 500 mL D5W¶ and administer over two hours. Shorter oxaliplatin administration schedules (eg, 1 mg/m$^2$ per minute) appear to be safe.[2] | Day 1 |
| Capecitabine$^{\diamond}$ | 1000 mg/m$^2$ orally per dose | Twice daily (total dose 2000 mg/m$^2$ per day), rounded to the nearest tablet size; swallow whole with water within 30 minutes after a meal, with each dose as close to 12 hours apart as possible. **Do not** cut or crush tablets.§ | Days 1 to 14 |
| Pembrolizumab | 200 mg IV | Dilute in NS or D5W¶ to a final concentration between 1 and 10 mg/mL and infuse over 30 minutes through a 0.2- to 5-micron sterile, nonpyrogenic, low-protein-binding inline or add-on filter. | Day 1, every 3 weeks |
| **OR** | | | |
| Pembrolizumab | 400 mg IV | Dilute in NS or D5W¶ to a final concentration between 1 and 10 | Day 1, every 6 weeks |

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| | | mg/mL and infuse over 30 minutes through a 0.2- to 5-micron sterile, nonpyrogenic, low-protein-binding inline or add-on filter. | |

**Pretreatment considerations:**

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| **Immune status** | ▪ Anti-PD-1 monoclonal antibodies generate an immune response that may aggravate underlying autoimmune disorders or prior immune-related adverse events. There are only limited data on the safety and efficacy of checkpoint inhibitors such as pembrolizumab in patients with an underlying autoimmune disorder.[3] Pembrolizumab should be used with extreme caution in such individuals. |
| **Emesis risk** | ▪ Oxaliplatin: MODERATE.<br>▪ Oral capecitabine: LOW.<br>▪ Pembrolizumab and trastuzumab: LOW TO MINIMAL.<br>▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults. |
| **Prophylaxis for infusion reactions** | ▪ There is no standard premedication regimen for oxaliplatin or pembrolizumab. Most clinicians do not routinely premedicate prior to the first trastuzumab dose. However, patients may be instructed to self-administer acetaminophen or an NSAID if flu-like symptoms develop within 24 hours of drug administration.<br>▪ Refer to UpToDate topics on infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy and infusion reactions to systemic chemotherapy. |
| **Vesicant/irritant properties** | ▪ Oxaliplatin is classified as an irritant, but can cause significant tissue damage (rare); avoid extravasation.<br>▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants. |
| **Infection prophylaxis** | ▪ Primary prophylaxis with G-CSF is not justified (estimated risk of febrile neutropenia <20%[1]).<br>▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation. |
| **Dose adjustment for baseline liver or kidney dysfunction** | ▪ Lower starting doses of oxaliplatin and capecitabine may be needed for kidney impairment.<br>▪ Refer to UpToDate topics on chemotherapy nephrotoxicity and dose |

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| | modification in patients with kidney impairment, conventional cytotoxic agents. |
| **Thyroid function tests** | ▪ Assess baseline thyroid function tests (TSH, FT4) prior to initiation of therapy and periodically during treatment. |
| **Maneuvers to prevent neurotoxicity** | ▪ Counsel patients to avoid exposure to cold during and for approximately 72 hours after each infusion of oxaliplatin. Prolongation of the oxaliplatin infusion time from two to six hours may mitigate acute neurotoxicity.<br>▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy. |
| **Cardiopulmonary issues** | ▪ Prolongation of the QTc interval and ventricular arrhythmias have been reported after oxaliplatin. ECG monitoring is recommended if therapy is initiated in patients with heart failure, bradyarrhythmias, coadministration of drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid oxaliplatin in patients with congenital long QT syndrome. Correct hypokalemia and hypomagnesemia prior to initiating oxaliplatin. Pulmonary toxicity is rarely reported with oxaliplatin.<br>▪ Trastuzumab is associated with cardiomyopathy; assess baseline LVEF prior to therapy and at least every three months during therapy.[4] Patients with heart failure, coronary artery disease, myocardial infarction in the prior six months, or baseline LVEF <50% were excluded from one study.[1] Trastuzumab may also cause serious pulmonary toxicity and should be used with caution in patients with pre-existing pulmonary disease.<br>▪ Cardiotoxicity observed with capecitabine includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure sudden death, electrocardiographic changes, and cardiomyopathy.<br>▪ Refer to UpToDate topics on cardiotoxicity of trastuzumab and other HER2-targeted agents and fluoropyrimidine-associated cardiotoxicity. |
| **Regulatory issues** | ▪ An FDA-approved patient medication guide, which is available with the United States Prescribing Information,[3] must be dispensed with pembrolizumab. |

**Monitoring parameters:**

- Obtain CBC with differential and platelet count prior to each treatment.
- Assess electrolytes and liver and kidney function every three weeks prior to each new treatment.

- Assess changes in neurologic function prior to each treatment.

- All patients should be closely monitored and evaluated for immune-mediated adverse effects at least every three weeks during therapy.
- Monitor for fatigue, colitis, hepatotoxicity, hypophysitis, adrenal insufficiency, hypo- or hyperthyroidism, nephrotoxicity, pneumonitis, hyperglycemia, and skin rash. Many other clinically relevant immune-mediated toxicities have been observed, which may involve any organ system or tissue, and may be severe or fatal.
- While immune-mediated toxicities generally occur during treatment with pembrolizumab, adverse reactions, including infusion-related reactions, may also develop weeks to months after therapy discontinuation.
- Refer to UpToDate topics on toxicities associated with checkpoint inhibitor immunotherapy.

- Assess cardiac function every three months during therapy or as clinically indicated.
- Refer to UpToDate topics on cardiotoxicity of trastuzumab and other HER2-targeted agents and fluoropyrimidine-associated cardiotoxicity.

- Monitor for infusion reactions during pembrolizumab infusion and during trastuzumab infusion. For pembrolizumab, interrupt infusion and permanently discontinue for severe or life-threatening infusion-related reactions, as indicated in the United States Prescribing Information.[3]

- Monitor for mucositis, diarrhea, and palmar-plantar erythrodysesthesia during treatment.
- Refer to UpToDate topics on oral toxicity associated with chemotherapy, cutaneous side effects of conventional chemotherapy agents, and enterotoxicity of chemotherapeutic agents.

- More frequent anticoagulant response (INR or prothrombin time) monitoring is necessary for patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy.

**Suggested dose modifications for toxicity:**

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| **Immune-mediated toxicity** | ▪ No dose reductions of pembrolizumab are recommended; treatment is withheld or discontinued to manage toxicities.[1]<br>▪ In general, if an immune-mediated adverse event is suspected, evaluate appropriately to confirm or exclude other causes. Based on the type and severity of the reaction, withhold treatment and administer systemic glucocorticoids. Upon resolution to ≤grade 1, initiate glucocorticoid taper. Immune-mediated adverse reactions that do not resolve with systemic glucocorticoids may be managed with other systemic immunosuppressants (based on limited data). Discontinue pembrolizumab permanently for any grade 4 or recurrent grade 3 immune-mediated adverse event or one that is life threatening, grade 3 pneumonitis, AST/ALT elevation >8 times ULN, total bilirubin elevation >3 |

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| | times ULN in patients with no hepatic tumor involvement, AST/ALT elevation to >10 times ULN for hepatitis with hepatic tumor involvement grade ≥2 myocarditis, grade 3 neurologic toxicity, suspected exfoliative dermatologic condition, severe (grade 3) or life-threatening (grade 4) infusion reactions, or if there is an inability to reduce glucocorticoid dose to 10 mg or less of prednisone equivalent per day within 12 weeks of initiating glucocorticoids.[3]<br>▪ Most pembrolizumab-associated rashes can be managed with topical corticosteroid creams.<br>▪ Guidelines for managing specific toxicities, including immune-mediated adverse events, are available in the United States Prescribing Information for pembrolizumab,[3] from ASCO,[5] from the MASCC,[6] from the NCCN,[7] and from the SITC.[8]<br>▪ Refer to UpToDate topics on toxicities associated with checkpoint inhibitor immunotherapy. |
| **Myelotoxicity** | ▪ A new cycle of treatment should not start until neutrophils recover to >1500/microL and platelets recover to >75,000/microL.[1] Interrupt capecitabine for any grade 2 or worse hematologic toxicity and delay treatment with both capecitabine and oxaliplatin until complete recovery or improvement to ≤grade 1.[9] Reduce the capecitabine dose by 25% in subsequent cycles at the first occurrence of a grade 2 or grade 3 toxicity, and by 50% at the second occurrence of a given grade 2 or grade 3 toxicity or at the first occurrence of a grade 4 event.[10] After recovery, reduce oxaliplatin to 100 mg/m$^2$ for any intracycle grade 3 or 4 neutropenia or thrombocytopenia. Discontinue capecitabine and oxaliplatin permanently if, despite dose reduction, hematologic toxicity occurs for the third time at grade 2 or grade 3, or a second time at grade 4. |
| **Neurotoxicity** | ▪ Withhold oxaliplatin for grade 3 to 4 paresthesias/dysesthesias and reduce dose by 25% upon resolution to grade 0 to 2.[1] The United State Prescribing Information recommends a dose reduction in oxaliplatin to 65 mg/m$^2$ for persistent grade 2 neurosensory events that do not resolve, and permanent discontinuation for persistent grade 3 neurosensory events.[11]<br>▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy. |
| **Gastrointestinal toxicity** | ▪ Interrupt capecitabine and delay oxaliplatin for any grade 2 or worse gastrointestinal toxicity; restart treatment only after complete recovery or improvement to ≤grade 1.[1,4,6] After recovery, reduce the dose of oxaliplatin to 100 mg/m$^2$ after the first episode of grade 2 or worse |

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| | diarrhea or mucositis. Reduce the capecitabine dose by 25% in subsequent cycles at the first occurrence of grade 2 or 3 toxicity, and by 50% at the second occurrence of a given grade 2 or grade 3 toxicity or at the first occurrence of a grade 4 event.[10] Discontinue capecitabine permanently if, despite dose reduction, a given toxicity occurs for the third time at grade 2 or grade 3, or a second time at grade 4.[1,6]<br>▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after capecitabine should prompt evaluation for DPD deficiency. Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents. |
| **Cardiotoxicity** | ▪ Assess LVEF at least every three months during trastuzumab.[4] In the original protocol, published as a supplement to the clinical report,[1] patients with any signs or symptoms of heart failure had trastuzumab held while receiving heart failure treatment. Asymptomatic declines in LVEF of ≥16 percentage points or ≥10 points to below the lower limit of normal had trastuzumab held. Reinitiation of treatment was allowed for symptom resolution and/or return of LVEF to baseline, without a specific timeline. The United States Prescribing Information suggests withholding trastuzumab for at least four weeks for LVEF ≥16% decrease from baseline or LVEF below normal limits and ≥10% decrease from baseline and repeat LVEF every four weeks. May resume trastuzumab treatment if LVEF returns to normal limits within four to eight weeks and remains at ≤15% decrease from baseline value. Discontinue permanently for persistent (>8 weeks) LVEF decline or for >3 incidents of treatment interruptions for cardiomyopathy.[4]<br>▪ There is no recommended dose for the resumption of capecitabine following development of cardiac toxicity, and the drug should be discontinued.<br>▪ Refer to UpToDate topics on cardiotoxicity of trastuzumab and other HER2-targeted agents and fluoropyrimidine-associated cardiotoxicity. |
| **Pulmonary toxicity** | ▪ Discontinue trastuzumab for serious pulmonary toxicity. Withhold oxaliplatin for unexplained pulmonary symptoms until interstitial lung disease or pulmonary fibrosis is excluded.<br>▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, molecularly targeted agents and pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents. |
| **Other toxicities (including hepatotoxicity)** | ▪ Interrupt capecitabine and delay oxaliplatin for any grade 2 or worse other non-neurologic toxicity (except alopecia); restart treatment only after complete recovery or improvement to ≤grade 1.[1,4,6] Patients with grade 3 or 4 hyperbilirubinemia may resume capecitabine once toxicity has reduced to grade ≤2, but at a reduced dose.[10] |

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| | ▪ Reduce the dose of oxaliplatin for subsequent cycles to 100 mg/m$^2$ for drug-related grade 3 toxicity. Reduce the capecitabine dose by 25% in subsequent cycles at the first occurrence of a grade 2 or grade 3 toxicity and by 50% at the second occurrence of a given grade 2 or grade 3 toxicity or at the first occurrence of a grade 4 event.[10] Discontinue capecitabine permanently if, despite dose reduction, a given toxicity occurs for the third time at grade 2 or grade 3, or a second time at grade 4. |
| **Doses of capecitabine and trastuzumab omitted for toxicity are not replaced or restored; instead the patient should resume with the next planned treatment cycle.[1]** | |
| **If there is a change in body weight of at least 10%, doses should be recalculated.** | |

**This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of systemic therapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.**

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HER2: human epidermal growth factor 2 receptor; IV: intravenous; NS: normal saline; D5W: 5% dextrose in water; PD-1: programmed cell death protein 1; NSAID: nonsteroidal anti-inflammatory drug; G-CSF: granulocyte-colony stimulating factors; TSH: thyroid-stimulating hormone; FT4: free thyroxine; QT: time between the start of the Q wave and the end of the T wave (heart electrical cycle); QTc: corrected QT; ECG: electrocardiogram; LVEF: left ventricular ejection fraction; FDA: US Food and Drug Administration; CBC: complete blood count; INR: international normalized ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ULN: upper limit normal; ASCO: American Society of Clinical Oncology; MASCC: Multinational Association of Supportive Care in Cancer; NCCN: National Comprehensive Cancer Network; SITC: Society for Immunotherapy of Cancer; DPD: dihydropyrimidine dehydrogenase; IHC: immunohistochemical; FISH: fluorescence in situ hybridization.

* High levels of HER2 overexpression, as determined by either 3+ IHC staining or positive FISH, are used to select patients for therapy with trastuzumab. Refer to UpToDate topics on initial systemic therapy for locally advanced unresectable and metastatic esophageal and gastric cancer.

¶ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

Δ Many centers routinely infuse oxaliplatin through a central venous catheter because of local pain with infusion into a peripheral vein.

◇ No capecitabine dose has been shown to be safe in patients with complete DPD deficiency, and data are insufficient to recommend a dose in patients with partial DPD activity.

§ Extemporaneous compounding of liquid dose forms has been reported,[12] but intravenous fluoropyrimidine alternatives may be more appropriate for patients who are unable to swallow the

capecitabine tablets.

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*References:*

1. *Janjigian Y, Kawazoe A, Yañez P, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. Nature 2021; 600:727.*
2. *Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: Oxaliplatin can be safely infused at a rate of 1 mg/m2/min. J Oncol Pract 2016; 12:e548.*
3. *Pembrolizumab. United States Prescribing Information. US National Library of Medicine. (Available at dailymed.nlm.nih.gov, accessed on December 13, 2022).*
4. *Trastuzumab injection. United States Prescribing Information. US National Library of Medicine. (Available at dailymed.nlm.nih.gov, accessed on December 13, 2022).*
5. *Schneider BJ, Naidoo J, Santomasso BD, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol 2021; 39:4073.*
6. *MASCC 2020 clinical practice recommendations for the management of immune-mediated adverse events from checkpoint inhibitors. (Available at link.springer.com/journal/520/topicalCollection, accessed on April 18, 2023).*
7. *NCCN guidelines for management of immunotherapy-related toxicities. (Available at nccn.org, accessed on April 18, 2023).*
8. *SITC cancer immunotherapy guidelines. (Available at sitcancer.org/research/cancer-immunotherapy-guidelines, accessed on April 18, 2023).*
9. *Nehls O, Oettle H, Hartmann JT, et al. Capecitabine plus oxaliplatin as first-line treatment in patients with advanced biliary system adenocarcinoma: a prospective multicentre phase II trial. Br J Cancer 2008; 98:309.*
10. *Capecitabine. United States Prescribing Information. US National Library of Medicine. (Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020896s044s045s046s047s048s049s050s051lbl.pdf, accessed December 20, 2022).*
11. *Oxaliplatin injection. United States Prescribing Information. US National Library of Medicine. (Available at dailymed.nlm.nih.gov, accessed on December 13, 2022).*
12. *Lam MS. Extemporaneous compounding of oral liquid dosage formulations and alternative drug delivery methods for anticancer drugs. Pharmacotherapy 2011; 31:164.*

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Graphic 141602 Version 1.0

## Chemotherapy regimens for metastatic pancreatic cancer: FOLFIRINOX[1]

**Cycle length:** 14 days.

| Drug | Dose and route | Administration | Given on days |
|---|---|---|---|
| Oxaliplatin¶ | 85 mg/m$^2$ IV | Dilute in 500 mL D5W$^\Delta$ and administer over two hours (prior to leucovorin). Shorter oxaliplatin administration schedules (eg, 1 mg/m$^2$ per minute) appear to be safe.[2] | Day 1 |
| Leucovorin◇ | 400 mg/m$^2$ IV | Dilute in 250 mL D5W$^\Delta$ and administer over two hours (after oxaliplatin). | Day 1 |
| Irinotecan§ | 180 mg/m$^2$ IV | Dilute in 500 mL D5W$^\Delta$ and administer over 90 minutes. Administer concurrent with the last 90 minutes of leucovorin infusion, in separate bags, using a Y-line connection. | Day 1 |
| Fluorouracil (FU) | 400 mg/m$^2$ IV bolus | Give undiluted (50 mg/mL) as a slow IV push over five minutes (administer immediately after leucovorin). | Day 1 |
| FU | 2400 mg/m$^2$ IV | Dilute in 500 to 1000 mL 0.9% NS or D5W$^\Delta$ and administer as a continuous IV infusion over 46 hours (begin immediately after FU IV bolus). To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL) or the total dose diluted in 100 to 150 mL NS.$^\Delta$ | Day 1 |

**Pretreatment considerations:**

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| **Emesis risk** | ▪ HIGH (>90% frequency of emesis).¥<br>▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults. |

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| **Prophylaxis for infusion reactions** | ▪ No standard premedication regimen.<br>▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy. |
| **Vesicant/irritant properties** | ▪ Oxaliplatin and FU are irritants, but oxaliplatin can cause significant tissue damage; avoid extravasation.<br>▪ Refer to UpToDate topics on extravasation injury from chemotherapy anc other non-antineoplastic vesicants. |
| **Infection prophylaxis** | ▪ Primary prophylaxis with G-CSF is not warranted. However, given the risk of grade 3 or 4 neutropenia (46%[1]), primary prophylaxis with G-CSF is used at many institutions.<br>▪ Refer to UpToDate topics on use of granulocyte colony stimulating factor in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation. |
| **Dose adjustment for baseline liver or kidney dysfunction** | ▪ A lower starting dose of oxaliplatin and irinotecan may be needed for severe kidney insufficiency.[3,4] A lower starting dose of irinotecan and FU may be needed for patients with hepatic impairment.[4,5]<br>▪ **NOTE:** We do not recommend administration of FOLFIRINOX unless serum bilirubin is normal.<br>▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with kidney insufficiency, conventional cytotoxic agents. |
| **Maneuvers to prevent neurotoxicity** | ▪ Pharmacologic methods to prevent/delay the onset of oxaliplatin-related neuropathy are controversial due to the absence of large clinical trials proving benefit. Counsel patients to avoid exposure to cold during and for approximately 48 hours after each infusion.[3] Prolongation of the oxaliplatin infusion time from two to six hours may mitigate acute neurotoxicity.<br>▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy. |
| **Cardiac issues** | ▪ QT prolongation and ventricular arrhythmias have been reported after oxaliplatin. ECG monitoring is recommended if therapy is initiated in patients with heart failure, bradyarrhythmias, coadministration of drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid oxaliplatin in patients with congenital long QT syndrome. Correct hypokalemia and hypomagnesemia prior to initiating oxaliplatin. |

**Monitoring parameters:**

- CBC with differential and platelet count prior to each treatment.
- Electrolytes (especially potassium and magnesium), and liver and kidney function prior to each treatment.
- Irinotecan is associated with early and late diarrhea, both of which may be severe.[4] For patients who develop abdominal cramping and/or diarrhea within 24 hours of receiving irinotecan, administer atropine (0.3 to 0.6 mg IV) and premedicate with atropine during later cycles. Patients must be instructed in the early use of loperamide for late diarrhea. Patients who develop diarrhea should be closely monitored, and supportive care measures (eg, fluid and electrolyte replacement, loperamide, antibiotics, etc) should be provided as needed.
- Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.
- Assess changes in neurologic function prior to each treatment.

**Suggested dose modifications for toxicity:**

**Myelotoxicity**

- Do not retreat unless neutrophil count is ≥1500/microL and platelets are ≥75,000/microL.
- **Neutropenia**
  - The following dose reduction guidelines for hematologic toxicity were provided in the original protocol:[1] If day 1 treatment delayed for granulocytes <1500/microL, or febrile neutropenia or grade 4 neutropenia >7 days: Reduce irinotecan dose to 150 mg/m$^2$ and eliminate bolus FU and leucovorin. For second occurrence: Reduce oxaliplatin dose to 60 mg/m$^2$. If nonrecovery after two-week delay or third occurrence of granulocytes <1500/microL on day 1, or febrile neutropenia or grade 4 neutropenia at any time during cycle, discontinue treatment.
- **Thrombocytopenia**
  - The following dose reduction guidelines for hematologic toxicity were provided in the original protocol:[1] If day 1 treatment delayed for platelet count <75,000/microL, reduce oxaliplatin dose to 60 mg/m$^2$ and reduce both the bolus and continuous infusion FU to 75% of original doses. For second occurrence, reduce irinotecan dose to 150 mg/m$^2$. If nonrecovery after two-week delay or third occurrence of platelets <75,000/microL, discontinue treatment. For grade 3 or 4 thrombocytopenia *during* treatment, reduce oxaliplatin dose to 60 mg/m$^2$ and the infusional FU dose to 75% of the original dose. For the second occurrence, reduce dose of irinotecan to 150 mg/m$^2$ and the dose of infusional FU an additional 25%. Discontinue treatment

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| | for third occurrence. |
| **Diarrhea** | ▪ Do not retreat with FOLFIRINOX until resolution of diarrhea for at least 24 hours without antidiarrheal medication. For diarrhea grade 3 or 4, or diarrhea with fever and/or grade 3 or 4 neutropenia, reduce irinotecan dose to 150 mg/m$^2$ and eliminate bolus FU. For second occurrence, reduce the oxaliplatin dose to 60 mg/m$^2$ and the continuous FU dose to 75% of original dose. Discontinue treatment for third occurrence.<br>▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency.<br>▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents. |
| **Mucositis or hand-foot syndrome** | ▪ For grade 3 to 4 toxicity, reduce dose of both bolus and infusional FU by 25%. |
| **Pulmonary toxicity** | ▪ Oxaliplatin has rarely been associated with pulmonary toxicity. Withhold oxaliplatin for unexplained pulmonary symptoms until interstitial lung disease or pulmonary fibrosis is excluded.<br>▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents. |
| **Neurologic toxicity** | ▪ For transient grade 3 paresthesias/dysesthesias or grade 2 symptoms lasting >7 days, decrease oxaliplatin dose by 25%.[3] Discontinue oxaliplatin for grade 4 or persistent grade 3 paresthesia/dysesthesia.<br>▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[5] |
| **Cardiotoxicity** | ▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[5] |
| **Other toxicity** | ▪ Any other toxicity ≥grade 2, except anemia and alopecia, can justify dose reduction if medically indicated.<br>▪ For other nonhematologic toxicities, if grade 2, hold treatment until ≤grade 1; if grade 3 or 4, hold treatment until ≤grade 2.[4] |
| **If there is a change in body weight of at least 10%, doses should be recalculated.** | |

**This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of**

**chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.**

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CBC: complete blood count; DPD: dihydropyrimidine dehydrogenase; D5W: 5% dextrose in water; ECG: electrocardiogram; G-CSF: granulocyte-colony stimulating factors; IV: intravenous; QT: time between the start of the Q wave and the end of the T wave (heart electrical cycle); NS: normal saline.

¶ Many centers routinely infuse oxaliplatin via central venous line because of local pain with infusion into a peripheral vein.

Δ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

◇ Leucovorin dose is given for d,l-racemic mixture.[6] Use half the dose for LEVOleucovorin (l-leucovorin).

§ A lower initial dose of irinotecan may be considered for patients with poor performance status, prior pelvic or abdominal radiotherapy, or increased bilirubin levels.[4] Whether a reduced starting dose is needed in patients who are homozygous for the UGT 1A1*28 allele (Gilbert syndrome) and whether testing for this allele should be carried out prior to starting irinotecan are controversial. Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.

¥ At many institutions, regimens that combine oxaliplatin with irinotecan on day 1 are considered highly emetogenic, warranting the use of a neurokinin-1 receptor antagonist on day 1. The National Comprehensive Cancer Network considers this and similar regimens as moderately emetogenic.

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*References:*

1. *Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364:1817.*
2. *Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: Oxaliplatin Can Be Safely Infused at a Rate of 1 mg/m2/min. J Oncol Pract 2016; 12:e459.*
3. *Oxaliplatin injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 30, 2016).*
4. *Irinotecan hydrochloride injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 30, 2016).*
5. *Fluorouracil injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 30, 2016).*
6. *Leucovorin calcium injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 30, 2016).*

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Graphic 79571 Version 33.0

## Chemotherapy regimens for gastrointestinal cancer: FOLFIRI[1]

| **Cycle length:** 14 days. | | | |
|---|---|---|---|
| **Drug** | **Dose and route** | **Administration** | **Given on days** |
| Irinotecan | 180 mg/m$^2$ IV¶ | Dilute in 500 mL D5W$^\Delta$ and administer over 90 minutes (can be administered concurrently with leucovorin via y-site connection). | Day 1 |
| Leucovorin$^\diamond$ | 400 mg/m$^2$ IV | Dilute in 250 mL D5W$^\Delta$ and administer over two hours. | Day 1 |
| Fluorouracil (FU), bolus$^\S$ | 400 mg/m$^2$ IV | Slow IV push over five minutes (administer immediately after leucovorin). | Day 1 |
| FU, infusional | 2400 mg/m$^2$ IV¥ | Dilute in 500 to 1000 mL D5W$^\Delta$ and administer over 46 hours (begin immediately after FU bolus). To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL) or the total dose can be diluted in 100 to 150 mL NS.$^\Delta$ | Day 1 |

| **Pretreatment considerations:** | |
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| **Emesis risk** | ▪ MODERATE.<br>▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults. |
| **Prophylaxis for infusion reactions** | ▪ There is no standard premedication regimen for prophylaxis of infusion reactions. |
| **Infection prophylaxis** | ▪ Primary prophylaxis with G-CSF is not justified (estimated risk of febrile neutropenia approximately 6%[1]).<br>▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation. |
| **Dose** | ▪ A lower starting dose of FU and irinotecan may be needed for patients with |

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| **adjustment for baseline liver or kidney dysfunction** | liver impairment. A lower starting dose of irinotecan may be needed for patients with severe kidney impairment.<br>▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with kidney insufficiency, conventional cytotoxic agents. |
| **Diarrhea** | ▪ Irinotecan is associated with early and late diarrhea, both of which may be severe. For patients who develop abdominal cramps and/or diarrhea within 24 hours of treatment, administer atropine (0.3 to 0.6 mg IV) and premedicate with atropine during later cycles. Patients must be instructed in the early use of loperamide as a treatment for late diarrhea.<br>▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency.<br>▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents. |

## Monitoring parameters:

- Obtain CBC with differential and platelet count prior to each treatment.
- Assess electrolytes and liver and kidney function prior to each treatment.
- Patients who develop diarrhea should be closely monitored and supportive care measures (eg, fluid and electrolyte replacement, loperamide, antibiotics, etc) provided as needed. Do not retreat until resolution of diarrhea for at least 24 hours without antidiarrheal medication.

## Suggested dose modifications for toxicity:

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| **Myelotoxicity** | ▪ Delay treatment until ANC is >1500/microL and the platelet count is >100,000/microL. United States Prescribing Information suggests irinotecan dose reduction for grade 2 or worse hematologic toxicity during a prior cycle.[2]<br>▪ A different approach is used by some clinicians. If treatment is delayed for two weeks or delayed for one week on two separate occasions, the day 1 FU bolus is eliminated. With the second occurrence, reduce the FU infusion dose by 20% and reduce irinotecan dose to 150 mg/m$^2$. |
| **Diarrhea** | ▪ Withhold treatment until resolution of diarrhea for at least 24 hours off antidiarrheal medications. Reduce irinotecan dose for patients with grade 2 or worse diarrhea during a prior treatment cycle.[2]<br>▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents. |
| **Other toxicity** | ▪ If grade 2, hold treatment until ≤grade 1; if grade 3 or 4, hold treatment |

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| | until ≤grade 2.[2] Withhold FU for grade 2 or worse diarrhea, and restart at a lower dose after complete resolution.[3] Reduce irinotecan dose for patients with grade 2 or worse other nonhematologic toxicities during a prior treatment cycle except anorexia, alopecia, or asthenia.[2] For grade 3 mucositis, eliminate FU bolus dose; prophylactic ice chips may be beneficial.<br>▪ Refer to UpToDate topics on oral toxicity associated with chemotherapy. |
| **Neurologic toxicity** | ▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[3] |
| **Cardiotoxicity** | ▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[3] |
| **If there is a change in body weight of at least 10%, doses should be recalculated.** | |

**This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.**

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ANC: absolute neutrophil count; CBC: complete blood count; DPD: dihydropyrimidine dehydrogenase; D5W: 5% dextrose in water; ECG: electrocardiogram; G-CSF: granulocyte-colony stimulating factors; IV: intravenous; NS: normal saline.

¶ A lower initial starting dose of irinotecan may be considered for patients with poor performance status, prior pelvic or abdominal radiotherapy, or increased bilirubin levels.[2] Whether a reduced starting dose is needed in patients who are homozygous for the UGT 1A1*28 allele (Gilbert syndrome) and whether testing for this allele should be carried out prior to starting irinotecan is controversial. Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.

Δ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

◇ Leucovorin dose is given for d,l-racemic mixture.[4] Use half the dose for LEVOleucovorin (l-leucovorin).

§ At many institutions, the day one bolus dose of FU is routinely omitted, starting with cycle 1, to improve tolerability in the setting of metastatic disease.

¥ If there is no grade 1 or worse toxicity 1 in cycles 1 and 2, some clinicians increase the dose to 3000 mg/m$^2$ starting with cycle 3.[1]

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*References:*

1. *Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004; 22:229.*
2. *Irinotecan hydrochloride injection. United States Prescribing Information. US National Library of Medicine. (Available online at www.dailymed.nlm.nih.gov, accessed on July 23, 2018).*
3. *Fluorouracil injection. United States Prescribing Information. US National Library of Medicine. (Available online at www.dailymed.nlm.nih.gov, accessed on July 23, 2018).*
4. *Leucovorin calcium injection. United States Prescribing Information. US National Library of Medicine. (Available online at www.dailymed.nlm.nih.gov, accessed on July 23, 2018).*

Graphic 76300 Version 39.0

## Chemotherapy regimens for advanced esophagogastric cancer: Epirubicin cisplatin, and fluorouracil (ECF)[1,2]

| Drug | Dose and route | Administration | Given on days |
|---|---|---|---|
| Epirubicin | 50 mg/m$^2$ IV | Administer into a free-flowing IV solution with NS,* generally over 3 to 20 minutes. | Day 1 |
| Cisplatin | 60 mg/m$^2$ IV | Dilute with 250 mL NS* and administer over two hours. Do not administer with aluminum needles or IV sets. | Day 1 |
| Fluorouracil (FU) | 200 mg/m$^2$ per day IV | Infuse through a central line as a continuous infusion via a portable infusion device. | Daily for up to six months |
| **Pretreatment considerations:** | | | |
| **Hydration** | ▪ Give IV fluid to establish a urine flow of at least 100 mL/hour for at least two hours prior to and two hours after cisplatin administration.<br>▪ Refer to UpToDate topics on cisplatin nephrotoxicity. | | |
| **Emesis risk** | ▪ Epirubicin plus cisplatin: HIGH; daily low-dose continuous infusion.<br>▪ FU: LOW.<br>▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults. | | |
| **Prophylaxis for infusion reactions** | ▪ There are no recommended premedications to prevent infusion reactions with the ECF regimen.<br>▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy. | | |
| **Vesicant/irritant properties** | ▪ Epirubicin is a vesicant; cisplatin is an irritant but can cause significant tissue damage. Avoid extravasation of either agent.<br>▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants. | | |
| **Infection prophylaxis** | ▪ Primary prophylaxis with G-CSF is not warranted (incidence of grade 3 or 4 febrile neutropenia was 9% in one trial;[3] in a second trial, 14% developed either febrile neutropenia or infection[1]).<br>▪ Refer to UpToDate topics on use of granulocyte colony stimulating | | |

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| | factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation. |
| **Dose adjustment for baseline liver or kidney dysfunction** | ▪ The optimal approach to cisplatin therapy in patients with preexisting kidney impairment is unknown. In the original ECF protocol, cisplatin was not given to patients with a GFR <40 mL/min, full-dose cisplatin was administered to patients with a GFR ≥60 mL/min, and if the GFR was between 40 and 60 mL/min, the dose of cisplatin (in mg) equaled the GFR value in mL/min.[2] Lower starting doses of epirubicin may be needed in patients with preexisting kidney or hepatic impairment.[4] Lower starting doses of FU may be needed with severe liver impairment.[5]<br>▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with kidney impairment, conventional cytotoxic agents. |
| **Cardiac issues** | ▪ Epirubicin is associated with dose-dependent cardiomyopathy, the incidence of which is related to cumulative dose. Assess baseline LVEF prior to initiating therapy. Epirubicin is contraindicated for patients with recent myocardial infarction, severe myocardial dysfunction, severe arrhythmias, or prior treatment with maximum cumulative doses of anthracyclines. In the original protocol, patients were excluded from receiving epirubicin if their baseline LVEF was less than 50%.[2] |

**Monitoring parameters:**

- CBC with differential and platelet count on day 1 prior to each treatment cycle.
- Assess basic metabolic panel including creatinine and liver function tests once per cycle on day 1 prior to each treatment cycle.
- Monitor for neurotoxicity prior to each treatment cycle.
- Monitor for hearing loss prior to each dose of cisplatin; audiometry as clinically indicated.
- Monitor cumulative epirubicin dose. Reassess LVEF periodically during ECF therapy as clinically indicated.
- Refer to UpToDate topics on clinical manifestations, monitoring, and diagnosis of anthracycline-induced cardiotoxicity and prevention and management of anthracycline cardiotoxicity.

| Suggested dose modifications for toxicity: | |
|---|---|
| **Myelotoxicity** | ▪ Hold epirubicin until the platelets are ≥100,000/microL and the ANC is ≥1500/microL.[4] In the original ECF protocol, cisplatin and epirubicin doses were delayed by one week or until myelosuppression was resolved if the platelet count was <100,000/microL or the total WBC was <2000/microL on day 1.[2] The dose of epirubicin was reduced by 25% for a second episode of treatment delay due to myelosuppression or for febrile neutropenia. There were no dose reductions for infusional FU based on blood counts, but the United States Prescribing Information recommends treatment discontinuation for neutropenia (WBC <3500/microL or rapidly declining) or platelet count <100,000/microL.[5] |
| **Kidney dysfunction** | ▪ Hold cisplatin until serum creatinine <1.5 mg/dL and/or BUN <25 mg/dL.[6] In the original trial of ECF, full-dose cisplatin was given each cycle if the estimated GFR was >60 mL/min, and the drug was held if the estimated GFR was <40 mL/min.[2] For an estimated GFR of 40 to 60 mL/min, the dose of cisplatin (in mg) was equivalent to the estimated GFR (in mL/min).[2] |
| **Mucositis or diarrhea** | ▪ In the original protocol, a treatment break from FU was recommended for grade 2 or worse diarrhea. Treatment was withheld until symptoms resolved, then restarted at 150 mg/m$^2$ per day for grade 2 toxicity, and at 100 mg/m$^2$ per day for grade 3 or 4 toxicity.[2]<br>▪ **NOTE:** Severe diarrhea and mucositis after FU should prompt evaluation for DPD deficiency.<br>▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents. |
| **Neurotoxicity** | ▪ Neuropathy usually is seen with cumulative doses of cisplatin >400 mg/m$^2$, although there is marked interindividual variation. Patients with mild neuropathy can continue to receive full cisplatin doses. If neuropathy interferes with function, the risk of potentially disabling neurotoxicity must be weighed against the benefit of continued treatment.<br>▪ Refer to UpToDate topics on overview of neurologic complications of conventional non-platinum cancer chemotherapy.<br>▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[5] |

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| **Palmar-plantar erythrodysesthesias** | ▪ In the original trial, FU was withheld for one week for any grade of palmar-plantar erythrodysesthesia and then restarted at a dose of 150 mg/m$^2$ per day.[2]<br>▪ Refer to UpToDate topics on cutaneous complications of conventiona chemotherapy agents. |
| **Cardiotoxicity** | ▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[5] |
| **Other toxicity** | ▪ Hold epirubicin until all nonhematologic toxicity resolves to ≤grade 1 [4] Reduce epirubicin dose by 25% for any grade 3/4 nonhematologic toxicity in previous cycles. |
| **If there is a change in body weight of at least 10%, doses should be recalculated.** | |

**This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.**

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ANC: absolute neutrophil count; BUN: blood urea nitrogen; CBC: complete blood count; DPD: dihydropyrimidine dehydrogenase; GFR: glomerular filtration rate; G-CSF: granulocyte colony stimulating factors; IV: intravenous; LVEF: left ventricular ejection fraction; NS: normal saline; WBC: white blood cell count.

* Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

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*References:*

1. *Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 1997; 15:261.*
2. *Findlay M, Cunningham D, Norman A, et al. A phase II study in advanced gastro-esophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). Ann Oncol 1994; 5:609.*
3. *Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358:36.*
4. *Epirubicin hydrochloride injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 6, 2011).*
5. *Fluorouracil injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 6, 2011).*
6. *Cisplatin injection, powder, lyophilized, for solution. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 6, 2011).*

Graphic 62502 Version 31.0

## Chemotherapy regimens for advanced esophagogastric cancer: Epirubicin cisplatin, and capecitabine (ECX)[1,2]

**Cycle length:** 21 days.

| Drug | Dose and route | Administration | Given on days |
|---|---|---|---|
| Epirubicin | 50 mg/m$^2$ IV | Administer into a free flowing IV solution with NS,* generally over 3 to 20 minutes. | Day 1 |
| Cisplatin | 60 mg/m$^2$ IV | Dilute with at least 250 mL NS* and administer over 120 minutes. Do not administer with aluminum needles or IV sets. | Day 1 |
| Capecitabine¶ | 625 mg/m$^2$ per dose by mouth | Twice daily (total daily dose 1250 mg/m$^2$). Swallow whole with water within 30 minutes after a meal, with each dose as close to 12 hours apart as possible. Do not cut or crush tablets.Δ | Days 1 through 21 |

**Pretreatment considerations:**

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|---|---|
| **Hydration** | ▪ Give IV fluid to establish a urine flow of at least 100 mL/hour for at least two hours prior to and two hours after cisplatin administration.<br>▪ Refer to UpToDate topics on cisplatin nephrotoxicity. |
| **Emesis risk** | ▪ Epirubicin plus cisplatin: HIGH.<br>▪ Oral capecitabine alone: LOW.<br>▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults. |
| **Prophylaxis for infusion reactions** | ▪ There are no recommended premedications to prevent infusion reactions.<br>▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy. |
| **Vesicant/irritant properties** | ▪ Epirubicin is a vesicant; cisplatin is an irritant but can cause significant tissue damage. Avoid extravasation of either agent.<br>▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants. |

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| **Infection prophylaxis** | ▪ Primary prophylaxis with G-CSF is not warranted (incidence of febrile neutropenia with ECX was 0 and 7% in two trials[1,2]).<br>▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation. |
| **Dose adjustment for baseline liver or kidney dysfunction** | ▪ The optimal approach to cisplatin therapy in patients with preexisting kidney impairment is unknown. In the original ECX protocol, patients were required to have GFR ≥60 mL/min and a serum creatinine within normal range.[2] Lower starting doses of capecitabine may be needed in patients with kidney impairment.[3] Lower starting doses of epirubicin may be needed in patients with preexisting kidney or hepatic impairment.[4]<br>▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with kidney impairment, conventional cytotoxic agents. |
| **Cardiac issues** | ▪ Epirubicin is associated with dose-dependent cardiomyopathy, the incidence of which is related to cumulative dose. Assess baseline LVEF prior to initiating therapy. Epirubicin is contraindicated for patients with recent myocardial infarction, severe myocardial dysfunction, severe arrhythmias, or prior treatment with maximum cumulative doses of anthracyclines. In the original protocol, patients were excluded from receiving epirubicin if their LVEF was below the normal range.[2] |

**Monitoring parameters:**

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|---|
| ▪ CBC with differential and platelet count on day 1 prior to each treatment cycle. |
| ▪ Assess basic metabolic panel including creatinine and liver function tests on day 1 prior to each treatment cycle. |
| ▪ Monitor for neurotoxicity prior to each treatment cycle. |
| ▪ Monitor for stomatitis, diarrhea, and palmar-plantar erythrodysesthesias during treatment. |
| ▪ Monitor for hearing loss prior to each dose of cisplatin; audiometry as clinically indicated. |
| ▪ Monitor cumulative epirubicin dose. Reassess LVEF periodically as clinically indicated.<br>▪ Refer to UpToDate topics on clinical manifestations, monitoring, and diagnosis of |

anthracycline-induced cardiotoxicity and prevention and management of anthracycline cardiotoxicity.

- Cardiotoxicity observed with capecitabine includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. These adverse reactions may be more common in patients with a prior history of coronary artery disease.
- Refer to UpToDate topics on cardiotoxicity of cancer chemotherapy agents other than anthracyclines, HER2-targeted agents, and fluoropyrimidines.

**Suggested dose modifications for toxicity:**

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|---|---|
| **Myelotoxicity** | ▪ Hold epirubicin until the platelets are ≥100,000/microL and the ANC is ≥1500/microL.[4] In the original ECX protocol, cisplatin and epirubicin doses were delayed by one week or until myelosuppression was resolved if the platelet count was <100,000/microL or the total WBC count was <2000/microL on day 1.[2] The dose of epirubicin was reduced by 25% for a second episode of treatment delay due to myelosuppression or for febrile neutropenia. There were no dose reductions for capecitabine based on blood counts. |
| **Kidney dysfunction** | ▪ Hold cisplatin until serum creatinine <1.5 mg/dL and/or BUN <25 mg/dL.[5] In the original trial of ECX, full-dose cisplatin was given if the estimated GFR was >60 mL/min, and the drug was held if the estimated GFR was <40 mL/min.[2] For an estimated GFR of 40 to 60 mL/min, the dose of cisplatin (in mg) was equivalent to the estimated GFR (in mL/min). |
| **Mucositis, diarrhea, nausea and vomiting** | ▪ In the original trial, capecitabine was stopped for grade 2 to 3 stomatitis, diarrhea, or nausea and vomiting.[2] If grade 3 toxicity wa controlled adequately within two days and after resolution of any grade 2 toxicity, capecitabine was continued at full dose. If grade 2 toxicity occurred a second time, the dose was reduced by 25%; a thirc time, by 50%; and if it occurred a fourth time, treatment was discontinued. If grade 3 toxicity took longer than two days to resolve, the capecitabine dose for the next cycle was reduced by 25%; if grade 3 toxicity recurred, the dose was reduced by 50%; and if it recurred, the drug was discontinued. For grade 4 mucositis, diarrhea, or nausea or vomiting, the drug was either discontinued or the dose reduced by 50%.[3]<br>▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after capecitabine should prompt evaluation for DPD deficiency.<br>▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic |

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| | agents. |
| **Neurotoxicity** | ▪ Neuropathy usually is seen with cumulative doses of cisplatin >400 mg/m$^2$, although there is marked interindividual variation. Patients with mild neuropathy can continue to receive full cisplatin doses. If neuropathy interferes with function, the risk of potentially disabling neurotoxicity must be weighed against the benefit of continued treatment.<br>▪ Refer to UpToDate topics on overview of neurologic complications of conventional non-platinum cancer chemotherapy. |
| **Palmar-plantar erythrodysesthesias** | ▪ In the original trial, capecitabine was withheld for grade 2 or worse palmar-plantar erythrodysesthesias until resolution and the subsequent doses reduced by 15% for grade 2, 30% for grade 3, and 50% for grade 4 toxicity.[2]<br>▪ Refer to UpToDate topics on cutaneous complications of conventiona chemotherapy agents. |
| **Other toxicity (including hepatotoxicity)** | ▪ Hold epirubicin until all nonhematologic toxicity resolved to ≤grade 1.[4] Reduce epirubicin dose by 25% for any grade 3/4 nonhematologic toxicity in previous cycles.<br>▪ For capecitabine:<br>• Grade 2: For the first, second, and third occurrence, hold capecitabine.[3] After resolution to grade 1 or less, resume treatment (first occurrence, no dosage adjustment; second occurrence, 75% of the starting dose; third occurrence, 50% of the starting dose). For the fourth occurrence of a grade 2 toxicity, discontinue capecitabine therapy.<br>• Grade 3: For the first and second occurrence, hold capecitabine therapy. After resolution to grade 1 or less, resume treatment at a reduced dose (first occurrence, 75% of the starting dose; second occurrence, 50% of the starting dose). For the third occurrence of a grade 3 toxicity, discontinue capecitabine.<br>• Grade 4: Discontinue capecitabine therapy. Alternatively, hold capecitabine therapy, and begin next treatment at 50% of the starting dose when toxicity resolves to grade 1 or less; discontinue treatment for first recurrence of grade 4 toxicity. |
| **Doses of capecitabine that are omitted for toxicity are not replaced or restored. Instead, the patient should resume the planned treatment cycles at the modified dose.** | |
| **If there is a change in body weight of at least 10%, doses should be recalculated.** | |

**This table is provided as an example of how to administer this regimen; there may be other**

**acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.**

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ANC: absolute neutrophil count; BUN: blood urea nitrogen; CBC: complete blood count; DPD: dihydropyrimidine dehydrogenase; GFR: glomerular filtration rate; G-CSF: granulocyte-colony stimulating factors; IV: intravenous; LVEF: left ventricular ejection fraction; NS: normal saline; WBC: white blood cell.

* Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).
¶ No capecitabine dose has been shown to be safe in patients with complete DPD deficiency, and data are insufficient to recommend a dose in patients with partial DPD activity.
Δ Extemporaneous compounding of liquid dosage forms has been recommended, but IV therapies may be more appropriate for patients with significant swallowing difficulty.

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*References:*

1. *Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358:36.*
2. *Sumpter K, Harper-Wynne C, Cunningham D, et al. Report of two protocol planned interim analyses in a randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer receiving ECF. Br J Cancer 2005; 92:1976.*
3. *Capecitabine. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 29, 2016).*
4. *Epirubicin hydrochloride injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 29, 2016).*
5. *Cisplatin injection, powder, lyophilized, for solution. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on August 29, 2016).*

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Graphic 53899 Version 37.0

## Chemotherapy regimens for advanced esophagogastric cancer: Epirubicin oxaliplatin, and capecitabine (EOX)[1,2]

**Cycle length:** 21 days.

| Drug | Dose and route | Administration | Given on days |
|---|---|---|---|
| Epirubicin | 50 mg/m$^2$ IV | Administer into a free-flowing IV solution with NS,* generally over 3 to 20 minutes. | Day 1 |
| Oxaliplatin | 130 mg/m$^2$ IV¶ | Dilute with 500 mL D5W* and administer over two hours. Shorter oxaliplatin administration schedules (eg, 1 mg/m$^2$ per minute) appear to be safe.[3] | Day 1 |
| Capecitabine$^{\Delta}$ | 625 mg/m$^2$ per dose by mouth | Twice daily; take with water within 30 minutes after a meal. Capecitabine tablets should be swallowed whole. Do not crush or cut tablets.◇ | Days 1 through 21 |

**Pretreatment considerations:**

| | |
|---|---|
| **Emesis risk** | ▪ Epirubicin plus oxaliplatin: MODERATE (30 to 90% risk of emesis).<br>▪ Oral capecitabine alone: LOW (10 to 30% risk of emesis).<br>▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults. |
| **Prophylaxis for infusion reactions** | ▪ There is no standard premedication regimen for prophylaxis of infusion reactions with this regimen.<br>▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy. |
| **Vesicant/irritant properties** | ▪ Epirubicin is a vesicant; oxaliplatin is an irritant but can cause significant tissue damage. Avoid extravasation of either agent.<br>▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants. |
| **Infection prophylaxis** | ▪ Primary prophylaxis with G-CSF is not warranted (incidence of febrile neutropenia with the EOX regimen was 10% in two trials[1,2]).<br>▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and |

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|---|---|
| | conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation. |
| **Dose adjustment for baseline liver or kidney dysfunction** | ▪ Lower starting doses of capecitabine and oxaliplatin may be needed in patients with kidney impairment.[4,5] Lower starting doses of epirubicin may be needed in patients with pre-existing kidney or hepatic impairment.[6]<br>▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with kidney insufficiency, conventional cytotoxic agents. |
| **Maneuvers to prevent neurotoxicity** | ▪ Pharmacologic methods to prevent/delay the onset of oxaliplatin-related neuropathy are controversial due to the absence of large clinical trials proving benefit. Counsel patients to avoid exposure to cold during and for approximately 48 hours after each infusion. Prolongation of the oxaliplatin infusion time from two to six hours may mitigate acute neurotoxicity.<br>▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy. |
| **Cardiac issues** | ▪ Epirubicin is associated with dose-dependent cardiomyopathy, the incidence of which is related to cumulative dose. Assess baseline LVEF prior to initiating therapy. Epirubicin is contraindicated for patients with recent myocardial infarction, severe myocardial dysfunction, severe arrhythmias, or prior treatment with maximum cumulative doses of anthracyclines. In the original EOX protocol, patients were excluded from receiving epirubicin if their LVEF was below the normal range.[2]<br>▪ QT prolongation and ventricular arrhythmias have been reported after oxaliplatin. ECG monitoring is recommended if therapy is initiated in patients with heart failure, bradyarrhythmias, coadministration of drugs known to prolong the QT interval, and electrolyte abnormalities. Avoid oxaliplatin in patients with congenital long QT syndrome. Correct hypokalemia and hypomagnesemia prior to initiating oxaliplatin. |

**Monitoring parameters:**

- CBC with differential and platelet count on day 1 prior to each treatment cycle.
- Assess electrolytes (especially magnesium and phosphate) and liver and kidney function once per cycle on day 1.

| | |
|---|---|
| ▪ Monitor for stomatitis, diarrhea, and palmar-plantar erythrodysesthesias during therapy. | |
| ▪ Monitor for neurotoxicity prior to each treatment cycle. | |
| ▪ Monitor cumulative epirubicin dose. Reassess LVEF periodically during EOX therapy as clinically indicated.<br>▪ Refer to UpToDate topics on clinical manifestations, monitoring, and diagnosis of anthracycline-induced cardiotoxicity and prevention and management of anthracycline cardiotoxicity. | |
| ▪ Cardiotoxicity observed with capecitabine includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. These adverse reactions may be more common in patients with a prior history of coronary artery disease.<br>▪ Refer to UpToDate topics on cardiotoxicity of cancer chemotherapy agents other than anthracyclines, HER2-targeted agents, and fluoropyrimidines. | |
| **Suggested dose modifications for toxicity:** | |
| **Myelotoxicity** | ▪ Hold epirubicin until the platelets are ≥100,000/microL and the ANC is ≥1500/microL. In the original EOX protocol, day 1 epirubicin doses were delayed until the platelet count was ≥100,000/microL and the total WBC count was ≥2000/microL.[2] The dose of epirubicin was reduced by 25% for a second episode of treatment delay due to myelosuppression or for febrile neutropenia. Oxaliplatin was delayed by one week if the neutrophil count was <1000/microL or the platelet count was <75,000/microL. After recovery from grade 2 to 4 thrombocytopenia or grade 3 or 4 neutropenia, the dose of oxaliplatin was reduced to 100 mg/$m^2$. There were no dose reductions for capecitabine based on blood counts. |
| **Mucositis, diarrhea, nausea and vomiting** | ▪ In the original protocol, capecitabine was stopped if patients developed grade 2 or 3 stomatitis, diarrhea, or nausea and vomiting.[2] If grade 3 toxicity was controlled adequately within two days, capecitabine was resumed at full dose after resolution to ≤grade 1 toxicity. If grade 2 toxicity recurred, the dose was reduced by 25%; a third time, by 50%, and after the fourth episode, treatment was discontinued. If grade 3 toxicity took longer than two days to resolve, the capecitabine dose for the next cycle was reduced by 25%; if grade 3 toxicity recurred, the dose was reduced by 50%, and if it recurred again, the drug was discontinued. For grade 4 mucositis, diarrhea, or nausea or vomiting, the drug was either discontinued or the dose reduced by 50%. For persistent grade 3 to 4 diarrhea or stomatitis after appropriate capecitabine reduction, the dose of oxaliplatin was |

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| | reduced to 100 mg/m$^2$.<br>▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after capecitabine should prompt evaluation for DPD deficiency.<br>▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents. |
| **Neurotoxicity** | ▪ In the original protocol, oxaliplatin was delayed for one week for persistent grade 1 or worse neuropathy.[2] After recovery of persisting grade 1 to 2 neuropathy between cycles, or for any grade 3 to 4 neuropathy lasting for 7 to 14 days, the dose of oxaliplatin was reduced to 100 mg/m$^2$. Omit oxaliplatin for persistent grade 3 to 4 neuropathy lasting longer than 14 days. |
| **Palmar-plantar erythrodysesthesias** | ▪ In the original trial, capecitabine was withheld for grade 2 or higher palmar-plantar erythrodysesthesias until resolution and the subsequent doses reduced by 15% for grade 2, 30% for grade 3, and 50% for grade 4 toxicity.[2]<br>▪ Refer to UpToDate topics on cutaneous side effects of conventional chemotherapy agents. |
| **Pulmonary toxicity** | ▪ Oxaliplatin has rarely been associated with pulmonary toxicity. Withhold oxaliplatin for unexplained pulmonary symptoms until interstitial lung disease or pulmonary fibrosis is excluded.<br>▪ Refer to UpToDate topics on pulmonary toxicity associated with antineoplastic therapy, cytotoxic agents. |
| **Other toxicity (including hepatotoxicity)** | ▪ Hold epirubicin until all nonhematologic toxicity resolves to ≤grade 1[6] Reduce epirubicin dose by 25% for any grade 3/4 nonhematologic toxicity in previous cycles.<br>▪ For capecitabine:<br>• Grade 2: For the first, second, and third occurrence, hold capecitabine.[4] After resolution to grade 1 or less, resume treatment (first occurrence, no dosage adjustment; second occurrence, 75% of the starting dose; third occurrence, 50% of the starting dose). For the fourth occurrence of a grade 2 toxicity, discontinue capecitabine therapy.<br>• Grade 3: For the first and second occurrence, hold capecitabine therapy. After resolution to grade 1 or less, resume treatment at a reduced dose (first occurrence, 75% of the starting dose; second occurrence, 50% of the starting dose). For the third occurrence of a grade 3 toxicity, discontinue capecitabine therapy.<br>• Grade 4: Discontinue capecitabine therapy. Alternatively, hold capecitabine therapy, and begin next treatment at 50% of the |

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| | starting dose when toxicity resolves to grade 1 or less; discontinue treatment for first recurrence of grade 4 toxicity.<br>• Patients with grade 3 or 4 hyperbilirubinemia may resume capecitabine once toxicity has reduced to grade ≤2, but at a reduced dose.[4] |
| **Doses of capecitabine that are omitted for toxicity are not replaced or restored. Instead, the patient should resume the planned treatment cycles at the modified dose.[4]** | |
| **If there is a change in body weight of at least 10%, doses should be recalculated.** | |

**This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.**

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ANC: absolute neutrophil count; CBC: complete blood count; DPD: dihydropyrimidine dehydrogenase; D5W: 5% dextrose in water; ECG: electrocardiogram; G-CSF: granulocyte-colony stimulating factors; IV: intravenous; LVEF: left ventricular ejection fraction; NS: normal saline; QT: time between the start of the Q wave and the end of the T wave (heart electrical cycle); WBC: white blood cell.

* Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies). Oxaliplatin is incompatible with normal saline, and a D5W flush is recommended prior to starting the drug infusion.

¶ Many centers routinely infuse oxaliplatin through a central venous line because of local pain with infusion into a peripheral vein.

Δ No capecitabine dose has been shown to be safe in patients with complete DPD deficiency, and data are insufficient to recommend a dose in patients with partial DPD activity.

◇ Extemporaneous compounding of liquid dosage forms has been recommended, but IV therapies may be more appropriate for patients with significant swallowing difficulty.

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*References:*

1. *Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358:36.*
2. *Sumpter K, Harper-Wynne C, Cunningham D, et al. Report of two protocol planned interim analyses in a randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer receiving ECF. Br J Cancer 2005; 92:1976.*
3. *Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: Oxaliplatin Can Be Safely Infused at a Rate of 1 mg/m2/min. J Oncol Pract 2016; 12:e459.*
4. *Capecitabine. United States Prescribing Information. US National Library of Medicine. (Available online at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020896s044s045s046s047s048s049s050s051lbl.pdf, accessed on December 20, 2022).*
5. *Oxaliplatin injection. United States Prescribing Information. US National Library of Medicine. (Available online at*

*dailymed.nlm.nih.gov, accessed on December 6, 2011).*

6. *Epirubicin hydrochloride injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 6, 2011).*

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Graphic 75288 Version 34.0

## Chemotherapy regimens for advanced esophagogastric cancer: Docetaxel cisplatin, and fluorouracil (DCF)[1]

**Cycle length:** 21 days.

| Drug | Dose and route | Administration | Given on days |
|---|---|---|---|
| Docetaxel | 75 mg/m$^2$ IV | Dilute in 250 mL NS* to a final concentration of 0.3 to 0.74 mg/mL and administer over 60 minutes. | Day 1 |
| Cisplatin | 75 mg/m$^2$ IV | Dilute in 250 mL NS* and administer over 60 minutes. Do not administer with aluminum needles or IV sets. | Day 1 |
| Fluorouracil (FU) | 750 mg/m$^2$ per day IV | Dilute in 500 to 1000 mL D5W* and administer as a continuous infusion over 24 hours. For use in an ambulatory infusion pump. To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL) or the total dose can be diluted in 100 to 150 mL NS.* | Days 1 through 5 |

**Pretreatment considerations:**

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| **Hydration** | ▪ IV fluid to establish a urine flow of at least 100 mL/hour for two hours before and two hours after cisplatin administration.<br>▪ Refer to UpToDate topics on cisplatin nephrotoxicity. |
| **Emesis risk** | ▪ HIGH (>90% frequency of emesis).<br>▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults. |
| **Prophylaxis for infusion reactions** | ▪ Premedicate with dexamethasone prior to docetaxel administration.[1]<br>▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy. |
| **Vesicant/irritant properties** | ▪ Docetaxel and cisplatin are irritants, but can cause significant tissue damage; avoid extravasation.[2,3]<br>▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants. |

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| **Infection prophylaxis** | ▪ Primary prophylaxis with G-CSF indicated (incidence of neutropenic fever 29%[1]).<br>▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation. |
| **Dose adjustment for baseline liver or kidney dysfunction** | ▪ Docetaxel should not be given if serum bilirubin is above the ULN, or i the AST and/or ALT >1.5 times the ULN concomitant with AP >2.5 time the ULN.[3] Dose modifications of FU may be needed for patients with hepatic impairment.[4] The optimal approach to cisplatin therapy in patients with preexisting kidney impairment is unknown; such patient were excluded from the original trial.[1]<br>▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with kidney impairment, conventional cytotoxic agents. |
| **Dose adjustment for known drug interactions** | ▪ Caution is required if administering docetaxel with strong CYP3A4 inhibitors.¶ According to the United States Prescribing Information, avoid the use of docetaxel with strong CYP3A4 inhibitors (if possible). I concomitant therapy cannot be avoided, monitor closely for toxicity and consider a docetaxel dose reduction.[3] Docetaxel dose reduction for concomitant therapies should be individualized based on patient factors (eg, performance status) and the intent of therapy (ie, curative or palliative).<br>▪ Refer to "Suggested dose modifications for toxicity" below. |

**Monitoring parameters:**

- Assess CBC with differential and platelet count prior to each cycle of treatment.
- Assess basic metabolic panel including creatinine and electrolytes, and liver function tests prior to each treatment cycle.
- Monitor for neurotoxicity, diarrhea, and palmar-plantar erythrodysesthesias prior to each treatment cycle.
- Monitor for hearing loss prior to each dose of cisplatin; audiometry as clinically indicated.
- Patients with kidney impairment, hyperuricemia, and bulky tumors are at risk for TLS and should undergo correction of dehydration and lowering of high serum uric acid levels prior to treatment initiation, and be closely monitored for TLS during and after treatment.

- Refer to UpToDate topics on tumor lysis syndrome.

| Suggested dose modifications for toxicity: | |
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| **Myelotoxicity** | ▪ Patients should not be retreated until neutrophils recover to >1500/microL and platelets recover to >100,000/microL.[3] If the platelet count declines to <25,000/microL during therapy, reduce subsequent doses of docetaxel by 20%. After the first episode of ANC <1000/microL lasting >7 days or febrile neutropenia or neutropenic infection despite G-CSF support, reduce docetaxel dose by 20%.[3,5] For a second episode, reduce subsequent doses of docetaxel by another 20%. |
| **Kidney dysfunction** | ▪ Hold cisplatin until serum creatinine <1.5 mg/dL and/or BUN <25 mg/dL.[2] For grade ≥2 nephrotoxicity during treatment (creatinine >1.5 times normal value despite adequate rehydration), creatinine clearance should be determined prior to next cycle and cisplatin dose reduced if <60 mL/min. |
| **Neurotoxicity** | ▪ Neuropathy usually is seen with cumulative doses of cisplatin >400 mg/m$^2$, although there is marked interindividual variation. Reduce cisplatin dose 20% for grade ≥2 peripheral neuropathy and discontinue for grade 3 neuropathy.[2,5]<br>▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy.<br>▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[6] |
| **Gastrointestinal toxicity** | ▪ Hold FU treatment for grade 3 or worse diarrhea and restart at a lowe dose after complete resolution. For the first episode of grade 3 diarrhea or grade 3 or 4 stomatitis, reduce FU by 20%; subsequent episodes, reduce docetaxel 20%.[3] First episode of grade 4 diarrhea, reduce both docetaxel and FU by 20%; subsequent episodes, discontinue treatment.<br>▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency.<br>▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents. |
| **Palmar-plantar erythrodysesthesia** | ▪ Hold FU for grade 2 or greater palmar-plantar erythrodysesthesia, anc reduce subsequent dose by 20%.[6]<br>▪ Refer to UpToDate topics on cutaneous complications of conventional |

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| | chemotherapy agents. |
| **Hepatotoxicity** | ▪ Docetaxel should not be given if serum bilirubin is above the ULN, or i the AST and/or ALT >1.5 times the ULN concomitant with AP >2.5 time the ULN.[3] For intracycle increases of AST/ALT >2.5 but ≤5 times the ULN, and AP <2.5 times the ULN **or** AST/ALT >1.5 to ≤5 times the ULN **and** AP >2.5 to ≤5 times the ULN, reduce docetaxel by 20%.[3] Discontinue docetaxel if AST/ALT >5 times the ULN **and/or** AP >5 time the ULN. |
| **Cardiotoxicity** | ▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[6] |
| **If there is a change in body weight of at least 10%, doses should be recalculated.** | |

**This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.**

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ALT: alanine aminotransferase; ANC: absolute neutrophil count; AP: alkaline phosphatase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CBC: complete blood count; CYP3A4: cytochrome P450 3A4; DPD: dihydropyrimidine dehydrogenase; D5W: 5% dextrose in water; ECG: electrocardiogram; G-CSF: granulocyte colony stimulating factors; IV: intravenous; NS: normal saline; TLS: tumor lysis syndrome; ULN: upper limit of normal.

* Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

¶ A list of strong and moderate CYP3A4 inhibitors is available as a separate table in UpToDate. Specific interactions may be determined by use of the drug interactions program included within UpToDate.

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*References:*

1. *Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. 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 2006; 24:4991.*
2. *Cisplatin injection, powder, lyophilized, for solution. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on March 10, 2011).*
3. *Docetaxel injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on March 15, 2022).*

4. *Floyd J, Mirza I, Sachs B, Perry MC. Hepatotoxicity of chemotherapy. Semin Oncol 2006; 33:50.*
5. *Ajani JA, Fodor MB, Tjulandin SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. J Clin Oncol 2005; 23:5660.*
6. *Fluorouracil injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on March 10, 2011).*

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Graphic 73324 Version 46.0

## Chemotherapy regimens for advanced esophagogastric cancer: Modified docetaxel, cisplatin, and fluorouracil (modified DCF)[1]

**Cycle length:** 14 days.

| Drug | Dose and route | Administration | Given on days |
|---|---|---|---|
| Docetaxel | 40 mg/m$^2$ IV | Dilute with 250 mL NS* to a final concentration of 0.3 to 0.74 mg/mL and administer over 60 minutes. | Day 1 |
| Leucovorin¶ | 400 mg/m$^2$ IV | Dilute with 250 mL D5W* and administer over two hours. | Day 1 |
| Fluorouracil (FU) | 400 mg/m$^2$ IV bolus | Slow IV push over five minutes. Administer immediately after leucovorin. | Day 1 |
| FU | 2000 mg/m$^2$ IV | Dilute with 500 to 1000 mL D5W* and administer by continuous infusion for 48 hours starting immediately after the FU bolus on day 1. To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL) or the total dose can be diluted in 100 to 150 mL NS.* | Day 1 |
| Cisplatin | 40 mg/m$^2$ IV | Dilute with 250 mL NS* and administer over 60 minutes. Do not administer with aluminum needles or IV sets. | Day 3 |

**Pretreatment considerations:**

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| **Hydration** | ▪ IV fluid to establish a urine flow of at least 100 mL/hour for at least two hours prior to and two hours after cisplatin administration.<br>▪ Refer to UpToDate topics on cisplatin nephrotoxicity. |
| **Emesis risk** | ▪ Day 1 and 2: LOW;<br>Day 3: HIGH.<br>▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults. |

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| **Prophylaxis for infusion reactions** | ▪ Premedicate with dexamethasone prior to docetaxel administration.<br>▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy. |
| **Vesicant/irritant properties** | ▪ Docetaxel and cisplatin are irritants but can cause significant tissue damage; avoid extravasation.<br>▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants. |
| **Infection prophylaxis** | ▪ Primary prophylaxis with G-CSF not justified (incidence of neutropenic fever approximately 7%[1]).<br>▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation. |
| **Dose adjustment for baseline liver or kidney dysfunction** | ▪ The optimal approach to cisplatin therapy in patients with pre-existing kidney impairment is unknown. Patients with serum creatinine >1.5 mg/dL were excluded from the original trial.[1] Docetaxel should not be given to patients with a serum bilirubin above the ULN or to those with transaminase elevations >1.5 times ULN in conjunction with AP >2.5 times ULN.[2] Lower starting doses of FU may be needed for severe hepatic impairment.<br>▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and chemotherapy nephrotoxicity and dose modification in patients with kidney insufficiency, conventional cytotoxic agents. |
| **Dose adjustment for known drug interactions** | ▪ Caution is required if administering docetaxel with strong CYP3A4 inhibitors.[Δ] According to the United States Prescribing Information, avoid the use of docetaxel with strong CYP3A4 inhibitors (if possible). If concomitant therapy cannot be avoided, monitor closely for toxicity and consider a docetaxel dose reduction.[2] Docetaxel dose reductions for concomitant therapies should be individualized based on patient factors (eg, performance status) and the intent of therapy (ie, curative or palliative).<br>▪ Refer to "Suggested dose modifications for toxicity" below. |

**Monitoring parameters:**

- Assess CBC with differential and platelet count on day 1 prior to each new course of treatment
- Assess basic metabolic panel including creatinine and electrolytes, and liver function tests

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| | prior to each new treatment course. |
| | ▪ Monitor for neurotoxicity, diarrhea, and fluid retention prior to each treatment cycle. |
| | ▪ Monitor for hearing loss prior to each dose of cisplatin; audiometry as clinically indicated. |
| | ▪ Patients with kidney impairment, hyperuricemia, and bulky tumors are at risk for TLS and should undergo correction of dehydration and lowering of high serum uric acid levels prior to treatment initiation, and be closely monitored for TLS during and after treatment.<br>▪ Refer to UpToDate topics on tumor lysis syndrome. |
| **Suggested dose modifications for toxicity:** | |
| **Myelotoxicity** | ▪ Patients should not be retreated with subsequent cycles of modified DCF until neutrophils recover to ≥1000/microL and platelets recover to >75,000/microL. Reduce docetaxel dose by 10 mg/m$^2$ for febrile neutropenia, grade 3 or 4 neutropenia for ≥7 days, or platelet count ≤75,000/microL on the day of treatment.[1] |
| **Nephrotoxicity** | ▪ Withhold cisplatin until serum creatinine is ≤2 mg/dL.[1,3] Reduce cisplatin dose by 10 mg/m$^2$ for serum creatinine of 1.8 or 1.9 mg/dL. |
| **Neurotoxicity** | ▪ Neuropathy usually is seen with cumulative doses of cisplatin >400 mg/m$^2$, although there is marked interindividual variation. Docetaxel can also cause both sensory and motor neuropathy, the incidence of which is related to cumulative dose. Patients with mild neuropathy can continue to receive full cisplatin and docetaxel doses. However, if the neuropathy interferes with function, the risk of potentially disabling neurotoxicity must be weighed against the benefit of continued treatment. The protocol recommended a 10 mg/m$^2$ reduction in cisplatin dose for grade 3 or 4 ototoxicity and a 10 mg/m$^2$ reduction in docetaxel dose for grade ≥2 peripheral neuropathy.[1]<br>▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[4] |
| **Gastrointestinal toxicity** | ▪ After resolution of toxicity, reduce FU and leucovorin doses for grade 3 or 4 diarrhea or stomatitis.[4] The protocol suggested initial dose reduction from 400 to 300 mg/m$^2$ for the bolus dose of both FU and leucovorin, and a reduction from 1000 to 800 mg/m$^2$ per day for the infusional FU.[1] Reduce cisplatin dose by 10 mg/m$^2$ for grade 4 nausea or vomiting or grade 3 nausea or vomiting for >5 days.<br>▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency. |

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| | ▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents. |
| **Hepatotoxicity** | ▪ Hold docetaxel for bilirubin 1.5 to 2.0 mg/dL **or** total bilirubin one to two times ULN, **or** for AST/ALT >5 times ULN, **or** AP >5 times ULN, **or** AST/ALT >2 but ≤5 times the ULN and AP >3 times ULN, **or** AST/ALT >1 to ≤2 times ULN and AP >5 times ULN.[1] Reduce docetaxel dose by 10 mg/m$^2$ if AST/ALT >2 but ≤5 times ULN and AP >1 but ≤3 times ULN **or** AST/ALT >1 but ≤2 times ULN and AP >3 but ≤5 times ULN.[1] |
| **Cardiotoxicity** | ▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[4] |
| **Other toxicity** | ▪ Hold chemotherapy for any other grade 3 to 4 nonhematologic toxicity (with exception of grade 3 electrolyte abnormalities or grade 3 anemia not associated with bleeding). |
| **If there is a change in body weight of at least 10%, doses should be recalculated.** | |

**This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.**

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ALT: alanine aminotransferase; AP: alkaline phosphatase; AST: aspartate aminotransferase; CBC: complete blood count; CYP3A4: cytochrome P450 3A4; D5W: 5% dextrose in water; DPD: dihydropyrimidine dehydrogenase; G-CSF: granulocyte-colony stimulating factors; IV: intravenous; NS: normal saline; TLS: tumor lysis syndrome; ULN: upper limit of normal.

* Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

¶ Leucovorin dose is given for d,l-racemic mixture.[5] Use one-half the dose for LEVOleucovorin (l-leucovorin).

Δ A list of strong and moderate CYP3A4 inhibitors is available as a separate table in UpToDate. Specific interactions may be determined by use of the drug interactions program included within UpToDate.

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*References:*

1. *Shah M, Janjigian YY, Stoller R, et al. Randomized Multicenter Phase II Study of Modified Docetaxel, Cisplatin, and Fluorouracil (DCF) Versus DCF Plus Growth Factor Support in Patients With Metastatic Gastric Adenocarcinoma: A Study of the US Gastric Cancer Consortium. J Clin Oncol 2015; 33:3874.*
2. *Docetaxel injection. United States Prescribing Information. US National Library of Medicine. (Available online at*

*dailymed.nlm.nih.gov, accessed on March 15, 2022).*
3. *Cisplatin injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 14, 2011).*
4. *Fluorouracil injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 14, 2011).*
5. *Leucovorin calcium injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 14, 2011).*

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Graphic 79612 Version 35.0

## Contributor Disclosures

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