

Esophageal and Esophagogastric Cancer Treatment Regimens

Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced health care team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are provided only to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data become available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Note: All recommendations are category 2A unless otherwise indicated.

► Preoperative Chemoradiation¹

REGIMEN	DOSING
Preferred Regimens	
Capecitabine and Oxaliplatin (Category 1) ^{2,4}	Days 1-5,8-12,15-19,22-26,29-33: Capecitabine 625mg/m ² orally twice daily Days 1,15,29: Oxaliplatin 85mg/m ² IV over 2 hours. Repeat cycle every 5 weeks for 1 cycle with radiation.
Fluorouracil and Oxaliplatin (Category 1) ^{5-9,a,b}	Day 1: Oxaliplatin 85mg/m ² IV over 2 hours, with: Day 1: Leucovorin 400mg/m ² IV over 2 hours, followed by: Day 1: Fluorouracil 400mg/m ² IV push over 24 hours, followed by: Days 1-2: Fluorouracil 800mg/m ² continuous IV infusion over 24 hours (1,600mg/m ² IV over 46-48 hours). Repeat cycle every 2 weeks for 3 cycles with radiation. OR Day 1: Oxaliplatin 85mg/m ² IV over 2 hours Days 1-4,8-11: Fluorouracil 300mg/m ² IV continuous infusion over 24 hours daily (1,200mg/m ² IV over 96 hours). Repeat cycle every 2 weeks for 3 cycles with radiation.
Paclitaxel and Carboplatin (Category 1) ^{10-13,c}	Day 1: Paclitaxel 50mg/m ² IV over 1 hour, followed by: Day 1: Carboplatin AUC 2 IV over 30 minutes. Repeat weekly for 5 weeks with radiation.
Other Recommended Regimens	
Capecitabine and Cisplatin (Category 1) ^{2,14,d}	Day 1: Cisplatin 30mg/m ² IV over 1 hour Days 1-5: Capecitabine 800mg/m ² orally twice daily. Repeat weekly for 5 weeks with radiation.
Fluorouracil and Cisplatin (Category 1) ^{5,15,16,d}	Days 1-5: Cisplatin 15mg/m ² IV over 15 minutes Days 1-5: Fluorouracil 800mg/m ² IV continuous infusion over 24 hours daily (4,000mg/m ² IV over 120 hours). Repeat cycle every 3 weeks for 2 cycles with radiation. OR Days 1,29: Cisplatin 75-100mg/m ² IV over 2 hours Days 1-4: Fluorouracil 750-1,000mg/m ² IV continuous infusion over 24 hours daily (3,000-4,000mg/m ² IV over 96 hours). Administer for one 5-week cycle with radiation.
Irinotecan and Cisplatin (Category 2B) ^{17,18,d}	Days 1,8,22,29: Cisplatin 30mg/m ² IV over 1 hour, followed by: Days 1,8,22,29: Irinotecan 65mg/m ² IV over 90 minutes. Repeat cycle every 5 weeks for 1 cycle with radiation.
Paclitaxel and Capecitabine (Category 2B) ^{2,11,19,20,c}	Day 1: Paclitaxel 45-50mg/m ² IV over 1 hour Days 1-5: Capecitabine 625- 825mg/m ² orally twice daily. Repeat cycle weekly for 5 weeks with radiation.
Paclitaxel and Fluorouracil (Category 2B) ^{5,11,19,c}	Day 1: Paclitaxel 45-50mg/m ² IV over 1 hour Days 1-5: Fluorouracil 300mg/m ² IV continuous infusion over 24 hours daily (1,500mg/m ² IV over 120 hours). Repeat cycle weekly for 5 weeks with radiation.

► Perioperative Chemotherapy¹ (Only for adenocarcinoma of the thoracic esophagus or EGJ)^e

Preferred Regimens	
Capecitabine and Oxaliplatin ^{2,3,21}	Day 1: Oxaliplatin 130mg/m ² IV over 2 hours Days 1-14: Capecitabine 1,000mg/m ² orally twice daily. Repeat cycle every 3 weeks for 3 cycles preoperatively and 3 cycles postoperatively for a total of 6 cycles.

continued

Esophageal and Esophagogastric Cancer Treatment Regimens

► Perioperative Chemotherapy¹ (Only for adenocarcinoma of the thoracic esophagus or EGJ)^e (continued)

REGIMEN	DOSING
Preferred Regimens (continued)	
Fluorouracil, Leucovorin, Oxaliplatin, and Docetaxel (FLOT) (Category 1) ^{5-7,22,23,a,b,f}	<p>Day 1: Docetaxel 50mg/m² over 1 hour</p> <p>Day 1: Oxaliplatin 85mg/m² IV over 2 hours, with:</p> <p>Day 1: Leucovorin 200mg/m² IV over 2 hours, followed by:</p> <p>Day 1: Fluorouracil 2,600mg/m² IV continuous infusion over 24 hours.</p> <p>Repeat cycle every 2 weeks for 4 cycles preoperatively and 4 cycles postoperatively for a total of 8 cycles.</p>
Fluorouracil and Oxaliplatin ^{5-7,24,25,a,b}	<p>Day 1: Oxaliplatin 85mg/m² IV over 2 hours, with:</p> <p>Day 1: Leucovorin 400mg/m² IV over 2 hours, followed by:</p> <p>Day 1: Fluorouracil 400mg/m² IV push, followed by:</p> <p>Days 1-2: Fluorouracil 1,200mg/m² IV continuous infusion over 24 hours daily (2,400mg/m² IV over 46-48 hours).</p> <p>Repeat cycle every 2 weeks for 3 cycles preoperatively and 3 cycles postoperatively for a total of 6 cycles (perioperative).</p> <p>OR</p> <p>Day 1: Oxaliplatin 85mg/m² IV over 2 hours, with:</p> <p>Day 1: Leucovorin 200mg/m² IV over 2 hours, followed by:</p> <p>Day 1: Fluorouracil 2,600mg/m² IV continuous infusion over 24 hours.</p> <p>Repeat cycle every 2 weeks for 3 cycles preoperatively and 3 cycles postoperatively for a total of 6 cycles (perioperative).</p>
Other Recommended Regimens	
Fluorouracil and Cisplatin (Category 1) ^{5,26,d}	<p>Day 1: Cisplatin 50mg/m² IV over 1 hour</p> <p>Days 1-2: Fluorouracil 1,000mg/m² IV over 24 hours daily (2,000mg/m² IV over 48 hours).</p> <p>Repeat cycle for 2 weeks for 4 cycles postoperatively for a total of 8 cycles (perioperative).</p>

► Preoperative Chemotherapy¹ (Only for adenocarcinoma of the thoracic esophagus or EGJ)^e

Fluorouracil and Cisplatin (Category 2B) ^{5,27,28,d}	<p>Day 1: Cisplatin 80mg/m² IV over 2 hours</p> <p>Days 1-4: Fluorouracil 1,000mg/m² IV continuous infusion over 24 hours daily (4,000mg/m² IV over 96 hours).</p> <p>Repeat cycle every 3 weeks for 2 cycles.</p>
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► Definitive Chemoradiation (Non-Surgical)¹

Preferred Regimens	
Capecitabine and Cisplatin (Category 1) ^{2,29,d}	<p>Day 1: Cisplatin 30mg/m² IV over 1 hour</p> <p>Days 1-5: Capecitabine 800mg/m² orally twice daily.</p> <p>Repeat weekly for 5 weeks with radiation.</p>
Capecitabine and Oxaliplatin (Category 1) ²⁻⁴	<p>Days 1-5,8-12,15-19,22-26,29-33: Capecitabine 625mg/m² orally twice daily</p> <p>Days 1,15,29: Oxaliplatin 85mg/m² IV over 2 hours.</p> <p>Administer for one 5-week cycle with radiation.</p>
Fluorouracil and Cisplatin (Category 1) ^{5,30,d}	<p>Day 1: Cisplatin 75-100mg/m² IV over 2 hours</p> <p>Days 1-4: Fluorouracil 750-1,000mg/m² IV continuous infusion over 24 hours daily (3,000 -4,000mg/m² IV over 96 hours).</p> <p>Repeat every 4 weeks for 2-4 cycles (2 cycles with concurrent radiation followed by 2 cycles without radiation).</p>
Fluorouracil and Oxaliplatin (Category 1) ^{5-8,31,a,b}	<p>Day 1: Oxaliplatin 85mg/m² IV over 2 hours, with:</p> <p>Day 1: Leucovorin 400mg/m² IV over 2 hours, followed by:</p> <p>Day 1: Fluorouracil 400mg/m² IV push, followed by:</p> <p>Days 1-2: Fluorouracil 800mg/m² continuous IV infusion over 24 hours daily (1,600mg/m² IV over 46-48 hours).</p> <p>Repeat cycle every 2 weeks for 3 cycles with radiation followed by 3 cycles without radiation.</p> <p>OR</p> <p>Days 1,15,29: Oxaliplatin 85mg/m² IV over 2 hours</p> <p>Days 1-33: Fluorouracil 180mg/m² IV continuous infusion over 24 hours daily.</p> <p>Administer for one 5-week cycle with radiation.</p>
Paclitaxel and Carboplatin ^{10-13,c}	<p>Day 1: Paclitaxel 50mg/m² IV over 1 hour, followed by:</p> <p>Day 1: Carboplatin AUC 2 IV over 30 minutes.</p> <p>Repeat weekly for 5 weeks with radiation.</p>

continued

Esophageal and Esophagogastric Cancer Treatment Regimens

► Definitive Chemoradiation (Non-Surgical)¹ (continued)

REGIMEN	DOSING
Other Recommended Regimens	
Cisplatin with Docetaxel ^{22,32,33,d,f}	Days 1-22: Docetaxel 60mg/m ² IV over 1 hour, followed by: Days 1-22: Cisplatin 60-80mg/m ² IV over 2 hours. Administer for one 5-week cycle with radiation. OR Day 1: Docetaxel 20-30mg/m ² IV over 1 hour, followed by: Day 1: Cisplatin 20-30mg/m ² IV over 1 hour. Repeat weekly for 5 weeks with radiation.
Cisplatin with Paclitaxel ^{11,34,c,d}	Days 1,8,15,22: Paclitaxel 60mg/m ² IV over 1 hour, followed by: Day 1: Cisplatin 75mg/m ² IV over 2 hours. Administer for one 4-week cycle with radiation.
Irinotecan and Cisplatin (Category 2B) ^{17,18,d}	Days 1,8,22,29: Cisplatin 30mg/m ² IV over 1 hour, followed by: Days 1,8,22,29: Irinotecan 65mg/m ² IV over 90 minutes. Administer for one 5-week cycle with radiation.
Paclitaxel and Capecitabine (Category 2B) ^{2,11,19,20,c}	Day 1: Paclitaxel 45-50mg/m ² IV over 1 hour Days 1 -5: Capecitabine 625-825mg/m ² orally twice daily. Repeat cycle weekly for 5 weeks with radiation.
Paclitaxel and Fluorouracil (Category 2B) ^{5,11,19,c}	Day 1: Paclitaxel 45-50mg/m ² IV over 1 hour Days 1-5: Fluorouracil 300mg/m ² IV continuous infusion over 24 hours daily (1,500mg/m ² IV over 120 hours). Repeat cycle weekly for 5 weeks with radiation.

► Postoperative Therapy^{1,g}

Preferred Regimens	
Nivolumab (Only after preoperative chemoradiation with R0 resection and residual disease) (Category 1) ³⁵⁻³⁷	Day 1: Nivolumab 240mg IV over 30 minutes Repeat cycle every 2 weeks for 8 cycles, followed by: Day 1: Nivolumab 480mg IV over 30 minutes. Repeat cycle every 4 weeks for 9 cycles or until maximum duration of 1 year.
Other Recommended Regimens	
Capecitabine and Oxaliplatin ^{2,3,38,39,h}	Days 1-14: Capecitabine 1,000mg/m ² orally twice daily Day 1: Oxaliplatin 130mg/m ² IV over 2 hours Repeat cycle every 3 weeks for 8 cycles.
Fluorouracil and Oxaliplatin ^{5-7,24,25,a,b,h}	Day 1: Oxaliplatin 85mg/m ² IV over 2 hours with: Day 1: Leucovorin 400mg/m ² IV over 2 hours, followed by: Day 1: Fluorouracil 400mg/m ² IV push, followed by: Days 1-2: Fluorouracil 1,200mg/m ² IV continuous infusion over 24 hours daily (2,400mg/m ² IV over 46-48 hours). Repeat cycle every 14 days for a maximum of 12 cycles. OR Day 1: Oxaliplatin 85mg/m ² IV over 2 hours, with: Day 1: Leucovorin 200mg/m ² IV over 2 hours, followed by: Day 1: Fluorouracil 2,600mg/m ² IV continuous infusion over 24 hours. Repeat cycle every 2 weeks for a maximum of 12 cycles.

► Postoperative Chemoradiation (including Chemotherapy)^{1,g}

Capecitabine ^{2,40,41}	Days 1-14: Capecitabine 750-1,000mg/m ² orally twice daily. Administer for one 3-week cycle preceding and 2 cycles following chemotherapy/radiation. With radiation: Days 1-5: Capecitabine 625-825mg/m ² orally twice daily. Repeat cycle weekly for 5 weeks with radiation.
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Esophageal and Esophagogastric Cancer Treatment Regimens

► Postoperative Chemoradiation (including Chemotherapy)^{1,9} (continued)

REGIMEN	DOSING
Fluorouracil ^{5,742-44,a}	<p>Day 1: Leucovorin 400mg/m² IV over 2 hours, followed by: Day 1: Fluorouracil 400mg/m² IV push, followed by: Days 1-2: Fluorouracil 1,200mg/m² IV continuous infusion over 24 hours daily (2,400mg/m² IV over 46-48 hours). Repeat cycle every 2 weeks for 2 cycles preceding and 4 cycles following chemotherapy/radiation.</p> <p>OR</p> <p>Days 1-5: Fluorouracil 200-250mg/m² IV continuous infusion over 24 hours daily (1,000-1,200mg/m² IV over 120 hours) Repeat cycle weekly for 5 weeks with radiation.</p>

► First-Line Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease¹ (where local therapy is not indicated; oxaliplatin is generally preferred over cisplatin due to lower toxicity)

Preferred Regimens (for HER2 Overexpression Positive Adenocarcinoma)	
Capecitabine and Cisplatin and Trastuzumab (Category 1) ^{2,45-47,d,i}	<p>Day 1: Cisplatin 80mg/m² IV over 2 hours Days 1-14: Capecitabine 1,000mg/m² orally twice daily. Repeat cycle every 3 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes first infusion, then 6mg/kg over 30 minutes beginning with cycle 2. Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Day 1: Cisplatin 80mg/m² IV over 2 hours Days 1-14: Capecitabine 1,000mg/m² orally twice daily. Repeat cycle every 3 weeks, with: Day 1: Trastuzumab 6mg/kg IV over 90 minutes first infusion, then 4mg/kg over 30 minutes beginning with cycle 2. Repeat cycle every 2 weeks.</p>
Capecitabine and Oxaliplatin and Trastuzumab ^{2,6,38,39,45,47,48,i}	<p>Day 1: Oxaliplatin 85mg /m² IV over 2 hours Days 1-14: Capecitabine 625mg/m² orally twice daily. Repeat cycle every 3 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes first infusion, then 6mg/kg over 30 minutes beginning with cycle 2. Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Day 1: Oxaliplatin 85mg /m² IV over 2 hours Days 1-14: Capecitabine 625mg/m² orally twice daily. Repeat cycle every 3 weeks, with: Day 1: Trastuzumab 6mg/kg IV over 90 minutes first infusion, then 4mg/kg over 30 minutes beginning with cycle 2. Repeat cycle every 2 weeks.</p> <p>OR</p> <p>Day 1: Oxaliplatin 130mg /m² IV over 2 hours Days 1-14: Capecitabine 1,000mg/m² orally twice daily. Repeat cycle every 3 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes first infusion, then 6mg/kg over 30 minutes beginning with cycle 2. Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Day 1: Oxaliplatin 130mg /m² IV over 2 hours Days 1-14: Capecitabine 1,000mg/m² orally twice daily. Repeat cycle every 3 weeks, with: Day 1: Trastuzumab 6mg/kg IV over 90 minutes first infusion, then 4mg/kg over 30 minutes beginning with cycle 2. Repeat cycle every 2 weeks.</p>

continued

Esophageal and Esophagogastric Cancer Treatment Regimens

► **First-Line Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease¹** (where local therapy is not indicated; oxaliplatin is generally preferred over cisplatin due to lower toxicity) (continued)

REGIMEN	DOSING
Preferred Regimens for HER2 Overexpression Positive Adenocarcinoma (continued)	
<p>Fluorouracil and Cisplatin and Trastuzumab (Category 1)^{5,7,25,27,28,45,47,49,a,d,i}</p>	<p>Day 1: Cisplatin 75 -100mg/m² IV over 2 hours Days 1-4: Fluorouracil 750 -1,000mg/m² IV continuous infusion over 24 hours daily (3,000-4,000mg/m² IV over 96 hours). Repeat cycle every 4 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes first infusion, then 6mg/kg over 30 minutes beginning with cycle 2. Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Day 1: Cisplatin 75 -100mg/m² IV over 2 hours Days 1-4: Fluorouracil 750 -1,000mg/m² IV continuous infusion over 24 hours daily (3,000-4,000mg/m² IV over 96 hours). Repeat cycle every 4 weeks, with: Day 1: Trastuzumab 6mg/kg IV over 90 minutes first infusion, then 4mg/kg over 30 minutes beginning with cycle 2. Repeat cycle every 2 weeks.</p> <p>OR</p> <p>Day 1: Cisplatin 50mg/m² IV over 1 hour Day 1: Leucovorin 200mg/m² IV over 2 hours Day 1: Fluorouracil 2,000mg/m² IV continuous infusion over 24 hours. Repeat cycle every 2 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes first infusion, then 6mg/kg over 30 minutes beginning with cycle 2. Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Day 1: Cisplatin 50mg/m² IV over 1 hour Day 1: Leucovorin 200mg/m² IV over 2 hours Day 1: Fluorouracil 2,000mg/m² IV continuous infusion over 24 hours. Repeat cycle every 2 weeks, with: Day 1: Trastuzumab 6mg/kg IV over 90 minutes first infusion, then 4mg/kg over 30 minutes beginning with cycle 2. Repeat cycle every 2 weeks.</p>
<p>Fluorouracil and Oxaliplatin and Trastuzumab^{5-7,24,25,28,45,47,a,b,i}</p>	<p>Day 1: Oxaliplatin 85mg/m² IV over 2 hours with: Day 1: Leucovorin 400mg/m² IV over 2 hours, followed by: Day 1: Fluorouracil 400mg /m² IV push, followed by: Days 1-2: Fluorouracil 1,200mg/m² IV continuous infusion over 24 hours daily (2,400mg /m² IV over 46-48 hours). Repeat cycle every 2 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes first infusion, then 6mg/kg over 30 minutes beginning with cycle 2. Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Day 1: Oxaliplatin 85mg/m² IV over 2 hours, with: Day 1: Leucovorin 400mg/m² IV over 2 hours, followed by: Day 1: Fluorouracil 400mg /m² IV push, followed by: Days 1-2: Fluorouracil 1,200mg/m² IV continuous infusion over 24 hours daily (2,400mg /m² IV over 46 -48 hours). Repeat cycle every 2 weeks, with: Day 1: Trastuzumab 6mg/kg IV over 90 minutes first infusion, then 4mg/kg over 30 minutes beginning with cycle 2. Repeat cycle every 2 weeks.</p> <p>OR</p> <p>Day 1: Oxaliplatin 85mg/m² IV over 2 hours, with: Day 1: Leucovorin 200mg/m² IV over 2 hours, followed by: Day 1: Fluorouracil 2,600mg/m² IV continuous infusion over 24 hours. Repeat cycle every 2 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes first infusion, then 6mg/kg over 30 minutes beginning with cycle 2. Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Day 1: Oxaliplatin 85mg/m² IV over 2 hours, with: Day 1: Leucovorin 200mg/m² IV over 2 hours, followed by: Day 1: Fluorouracil 2,600mg/m² IV continuous infusion over 24 hours. Repeat cycle every 2 weeks, with: Day 1: Trastuzumab 6mg/kg IV over 90 minutes first infusion, then 4mg/kg over 30 minutes beginning with cycle 2. Repeat cycle every 2 weeks.</p>

continued

Esophageal and Esophagogastric Cancer Treatment Regimens

► **First-Line Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease¹** (where local therapy is not indicated; oxaliplatin is generally preferred over cisplatin due to lower toxicity) (continued)

REGIMEN	DOSING
Preferred Regimens for HER2 Overexpression Negative Adenocarcinoma	
Capecitabine and Cisplatin ^{2,46,d}	Day 1: Cisplatin 80mg/m ² IV over 2 hours Days 1-14: Capecitabine 1,000mg/m ² orally twice daily. Repeat cycle every 3 weeks.
Capecitabine, Cisplatin, and Pembrolizumab (PDL1 CPS > 10) (Category 1) ^{2,46,50,51,d,e,j}	Day 1: Pembrolizumab 200mg IV over 30 minutes Repeat cycle for 3 weeks up to 2 years of therapy, with: Day 1: Cisplatin 80mg/m ² IV over 2 hours Days 1-14: Capecitabine 1,000mg/m ² orally twice daily. Repeat cycle every 3 weeks for a maximum of 6 cycles (18 weeks).
Capecitabine and Oxaliplatin ^{2,3,21,39,48}	Day 1: Oxaliplatin 85mg /m ² IV over 2 hours Days 1-14: Capecitabine 625mg/m ² orally twice daily. Repeat cycle every 3 weeks. OR Days 1-14: Capecitabine 1,000mg/m ² orally twice daily Day 1: Oxaliplatin 130mg /m ² IV over 2 hours. Repeat cycle every 3 weeks for 8 cycles.
Capecitabine, Oxaliplatin, and Nivolumab (PDL1 CPS > 5) for adenocarcinoma only (Category 1) ^{2,3,35,52,e}	Day 1: Nivolumab 360mg IV over 30 minutes Day 1: Oxaliplatin 130mg/m ² over 2 hours Days 1-14: Capecitabine 1,000mg/m ² orally twice daily. Repeat cycle every 3 weeks.
Capecitabine, Oxaliplatin, and Pembrolizumab (PDL1 CPS > 10) ^{2,3,39,50,51,e,j}	Day 1: Pembrolizumab 200mg IV over 30 minutes Repeat cycle for 3 weeks up to 2 years of therapy, with: Day 1: Oxaliplatin 130mg/m ² over 2 hours Days 1-14: Capecitabine 1,000mg/m ² orally twice daily. Repeat cycle every 3 weeks for a maximum of 6 cycles (18 weeks).
Fluorouracil and Cisplatin ^{5,25,27,28,49,d}	Day 1: Cisplatin 75-100mg/m ² IV over 2 hours Days 1-4: Fluorouracil 750 1,000mg/m ² IV continuous infusion over 24 hours daily (3,000-4,000mg/m ² IV over 96 hours). Repeat cycle every 4 weeks. OR Day 1: Cisplatin 50mg/m ² IV over 60 minutes Day 1: Leucovorin 200mg/m ² IV over 2 hours, followed by: Day 1: Fluorouracil 2,000mg/m ² IV continuous infusion over 24 hours. Repeat cycle every 2 weeks.
Fluorouracil, Cisplatin, and Pembrolizumab (PDL1 CPS > 10) (Category 1) ^{5,50,51,d,e,j}	Day 1: Pembrolizumab 200mg IV over 30 minutes. Repeat cycle for 3 weeks up to 2 years of therapy, with: Day 1: Cisplatin 85mg/m ² IV over 2 hours Days 1-5: Fluorouracil 800mg/m ² IV continuous infusion over 24 hours daily (4,000mg/m ² IV over 120 hours). Repeat cycle every 3 weeks for a maximum of 6 cycles.
Fluorouracil and Oxaliplatin ^{5-7,24,25,a,b}	Day 1: Oxaliplatin 85mg/m ² IV over 2 hours with: Day 1: Leucovorin 400mg/m ² IV over 2 hours, followed by: Day 1: Fluorouracil 400mg /m ² IV push, followed by: Days 1-2: Fluorouracil 1,200mg/m ² IV continuous infusion over 24 hours daily (2,400mg /m ² IV over 46-48 hours). Repeat cycle every 2 weeks. OR Day 1: Oxaliplatin 85mg/m ² IV over 2 hours, with: Day 1: Leucovorin 200mg/m ² IV over 2 hours, followed by: Day 1: Fluorouracil 2,600mg/m ² IV continuous infusion over 24 hours. Repeat cycle every 2 weeks

continued

Esophageal and Esophagogastric Cancer Treatment Regimens

► **First-Line Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease¹** (where local therapy is not indicated; oxaliplatin is generally preferred over cisplatin due to lower toxicity) (continued)

REGIMEN	DOSING
Preferred Regimens for HER2 Overexpression Negative Adenocarcinoma (continued)	
Fluorouracil, Oxaliplatin, and Nivolumab (PDL1 CPS > 5) for adenocarcinoma only (Category 1) ^{5-7,24,35,52,a,b,e,j}	<p>Day 1: Nivolumab 240mg IV over 30 minutes</p> <p>Day 1: Oxaliplatin 85mg/m² IV over 2 hours, with:</p> <p>Day 1: Leucovorin 400mg/m² IV over 2 hours, followed by:</p> <p>Day 1: Fluorouracil 400mg /m² IV push, followed by:</p> <p>Days 1-2: Fluorouracil 1,200mg/m² IV continuous infusion over 24 hours daily (2,400mg/m² IV over 46-48 hours).</p> <p>Repeat cycle every 2 weeks.</p>
Fluorouracil, Oxaliplatin, and Pembrolizumab (PDL1 CPS > 10) ^{5-7,24,50,51,a,b,e,j}	<p>Day 1: Pembrolizumab 200mg IV over 30 minutes.</p> <p>Repeat cycle for 3 weeks up to 2 years of therapy, with:</p> <p>Day 1: Oxaliplatin 85mg/m² IV over 2 hours, with:</p> <p>Day 1: Leucovorin 400mg/m² IV over 2 hours, followed by:</p> <p>Day 1: Fluorouracil 400mg /m² IV push, followed by:</p> <p>Days 1-2: Fluorouracil 1,200mg/m² IV continuous infusion over 24 hours daily (2,400mg/m² IV over 46-48 hours).</p> <p>Repeat cycle every 2 weeks for a maximum of 9 cycles (total 18 weeks).</p>
Other Recommended Regimens (Traztuzumab should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma)⁴⁷	
Capecitabine ^{2,53}	<p>Days 1-14: Capecitabine 1,000-1,250mg/m² orally twice daily.</p> <p>Repeat cycle every 3 weeks.</p>
Docetaxel ^{22,23,54,f}	<p>Day 1: Docetaxel 70-100mg/m² IV over 1 hour.</p> <p>Repeat cycle every 3 weeks.</p>
Docetaxel, Carboplatin, and Fluorouracil (Category 2B) ^{2,5,22,55,f}	<p>Day 1: Docetaxel 75mg/m² IV over 1 hour</p> <p>Day 2: Carboplatin AUC 6 IV over 30 minutes</p> <p>Days 1-3: Fluorouracil 1,200mg/m² IV continuous infusion over 24 hours daily (3,600mg/m² over 72 hours).</p> <p>Repeat cycle every 3 weeks.</p>
Docetaxel and Cisplatin ^{19,22,56-58,d,f}	<p>Day 1: Docetaxel 70-85mg/m² IV over 1 hour, followed by:</p> <p>Day 1: Cisplatin 70-75mg/m² over 2 hours.</p> <p>Repeat cycle every 3 weeks.</p>
Docetaxel, Cisplatin, and Fluorouracil ^{5-7,22,59,d,f}	<p>Day 1: Docetaxel 40mg/m² IV over 1 hour</p> <p>Day 1: Leucovorin 400mg/m² IV over 2 hours, followed by:</p> <p>Day 1: Fluorouracil 400mg /m² IV push, followed by:</p> <p>Days 1-2: Fluorouracil 1,000mg/m² IV continuous infusion over 24 hours daily (2,000mg /m² IV over 48 hours)</p> <p>Day 3: Cisplatin 40mg/m² IV over 1 hour.</p> <p>Repeat cycle every 2 weeks.</p>
Docetaxel, Oxaliplatin, and Fluorouracil ^{5,6,22,60,f}	<p>Day 1: Docetaxel 50mg/m² IV over 1 hour</p> <p>Day 1: Oxaliplatin 85mg/m² IV over 2 hours</p> <p>Days 1-2: Fluorouracil 1,200mg/m² IV continuous infusion over 24 hours daily (2,400mg/m² over 48 hours).</p> <p>Repeat cycle every 2 weeks.</p>
Fluorouracil ^{5,7,48,49,61,62,a}	<p>Days 1-5: Fluorouracil 800mg/m² IV continuous infusion over 24 hours daily (4,000mg/m² over 120 hours).</p> <p>Repeat cycle every 4 weeks.</p> <p>OR</p> <p>Day 1: Leucovorin 400mg/m² IV over 2 hours, followed by:</p> <p>Day 1: Fluorouracil 400mg/m² IV push, followed by:</p> <p>Days 1-2: Fluorouracil 1,200mg/m² IV continuous infusion over 24 hours daily (2,400mg/m² over 46-48 hours).</p> <p>Repeat cycle every 2 weeks.</p>

continued

Esophageal and Esophagogastric Cancer Treatment Regimens

► First-Line Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease¹ (where local therapy is not indicated; oxaliplatin is generally preferred over cisplatin due to lower toxicity) (continued)

REGIMEN	DOSING
Other Recommended Regimens (Trastuzumab should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma)⁴⁷ (continued)	
Fluorouracil and Irinotecan ^{5,7,17,63-66,a,k}	<p>Days 1,8,15,22,29,36: Irinotecan 80mg/m² IV over 90 minutes weekly, followed by: Days 1,8,15,22,29,36: Leucovorin 500mg/m² over 2 hours weekly Days 1,8,15,22,29,36: Fluorouracil 2,000mg/m² IV continuous infusion over 24 hours weekly. Repeat cycle every 8 weeks (6 weeks on followed by 2 weeks off treatment). OR Days 1: Irinotecan 180mg/m² IV over 90 minutes, with: Days 1: Leucovorin 400mg/m² over 90 minutes, followed by: Days 1: Fluorouracil 400mg/m² IV push, followed by: Days 1-2: Fluorouracil 1,200mg/m² IV continuous infusion over 24 hours daily (2,400mg/m² IV over 46-48 hours). Repeat cycle every 2 weeks.</p>
Paclitaxel ^{11,67-70,c}	<p>Day 1: Paclitaxel 135-250mg/m² IV over 3 hours. Repeat cycle every 3 weeks. OR Days 1,8,15,22: Paclitaxel 80mg/m² IV over 1 hour. Repeat cycle every 4 weeks. OR Days 1,8,15: Paclitaxel 80mg/m² IV over 1 hour. Repeat cycle every 4 weeks.</p>
Paclitaxel and Carboplatin ^{10,11,71,c}	<p>Day 1: Paclitaxel 200mg/m² IV over 3 hours, followed by: Day 1: Carboplatin AUC 5 IV over 30 minutes. Repeat cycle every 3 weeks.</p>
Paclitaxel and Cisplatin ^{11,72,c,d}	<p>Day 1: Paclitaxel 135-200mg/m² IV over 3 hours, followed by: Day 2: Cisplatin 75mg/m² IV over 2 hours. Repeat cycle every 3 weeks. OR Day 1: Paclitaxel 90mg/m² IV over 30 minutes, followed by: Day 1: Cisplatin 50mg/m² IV over 1 hour. Repeat cycle every 2 weeks.</p>

► Second-Line or Subsequent Systemic Therapy for Unresectable, Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated; dependent on prior therapy and PS)^e

Preferred Regimens	
Docetaxel ^{22,23,54,74,f} (Category 1)	<p>Day 1: Docetaxel 75-100mg/m² IV over 1 hour. Repeat cycle every 3 weeks.</p>
Fam-trastuzumab deruxtecan-nxki (for HER2 overexpression positive adenocarcinoma) ⁷⁵⁻⁷⁷	<p>Day 1: Fam-trastuzumab deruxtecan-nxki 6.4mg/kg IV. Repeat cycle every 3 weeks.</p>
Fluorouracil and Irinotecan ^{5,7,17,64-66,a,k}	<p>Days 1: Irinotecan 180mg/m² IV over 90 minutes, with: Days 1: Leucovorin 400mg/m² over 90 minutes, followed by: Days 1: Fluorouracil 400mg/m² IV push, followed by: Days 1-2: Fluorouracil 1,200mg/m² IV continuous infusion over 24 hours daily (2,400mg/m² IV over 46-48 hours). Repeat cycle every 2 weeks.</p>
Irinotecan (Category 1) ^{17,65,69,78,79}	<p>Day 1: Irinotecan 150-180mg/m² IV over 90 minutes. Repeat cycle every 2 weeks. OR Day 1: Irinotecan 250-350mg/m² IV over 90 minutes. Repeat cycle every 3 weeks. OR Days 1,8: Irinotecan 125mg/m² IV over 90 minutes. Repeat cycle every 3 weeks.</p>

continued

Esophageal and Esophagogastric Cancer Treatment Regimens

► Second-Line or Subsequent Systemic Therapy for Unresectable, Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated; dependent on prior therapy and PS)^e (continued)

REGIMEN	DOSING
Preferred Regimens (continued)	
Paclitaxel (Category 1) ^{11,67-70,c}	<p>Day 1: Paclitaxel 135-250mg/m² IV 1 hour. Repeat cycle 3 weeks.</p> <p>OR</p> <p>Days 1,8,15,22: Paclitaxel 80mg/m² IV over 1 hour. Repeat cycle 4 weeks.</p> <p>OR</p> <p>Days 1,8,15: Paclitaxel 80mg/m² IV over 1 hour. Repeat cycle 4 weeks.</p>
Pembrolizumab (for second-line therapy for esophageal squamous cell carcinoma with PDL1 CPS > 10 (Category 1); for third-line or subsequent therapy for esophageal and EGJ adenocarcinoma with PDL1 CPS >1) ^{50,80-84,e,j}	<p>Day 1: Pembrolizumab 200mg IV over 30 minutes. Repeat cycle for 3 weeks.</p> <p>OR</p> <p>Day 1: Pembrolizumab 400mg IV over 30 minutes. Repeat cycle for 6 weeks.</p>
Nivolumab (for esophageal squamous cell carcinoma) (Category 1) ^{35-37,j}	<p>Day 1: Nivolumab 240mg IV over 30 minutes. Repeat cycle every 2 weeks.</p> <p>OR</p> <p>Day 1: Nivolumab 480mg IV over 30 minutes. Repeat cycle every 4 weeks.</p>
Ramucirumab and Paclitaxel (Category 1 for EGJ adenocarcinoma; Category 2A for esophageal adenocarcinoma) ^{11,85,86,c,e,l}	<p>Days 1,15: Ramucirumab 8mg/kg IV over 1 hour Days 1,8,15: Paclitaxel 80mg/m² IV over 1 hour. Repeat cycle 4 weeks.</p>
Trifluridine and Tipiracil (for third-line or subsequent therapy for EGJ adenocarcinoma) (Category 1) ^{87,88,e}	<p>Days 1-5 and 8-12: Trifluridine and Tipiracil 35mg/m² (maximum 80mg) based on the trifluridine component orally twice daily. Total dose should not exceed 160mg/day. Repeat cycle every 4 weeks.</p>
Other Recommended Regimens	
Docetaxel and Irinotecan (Category 2B) ^{17,22,89,f}	<p>Days 1,8: Docetaxel 35mg/m² IV over 1 hour, followed by: Days 1,8: Irinotecan 50mg/m² IV over 90 minutes. Repeat cycle every 3 weeks.</p>
Fluorouracil and Irinotecan and Ramucirumab (for adenocarcinoma) ^{5,7,17,85,90-92,a,k,l}	<p>Day 1: Ramucirumab 8mg/kg IV over 1 hour Day 1: Irinotecan 180mg/m² IV over 90 minutes, with: Day 1: Leucovorin 400mg/m² over 90 minutes, followed by: Day 1: Fluorouracil 400mg/m² IV push, followed by: Days 1 -2: Fluorouracil 1,200mg/m² IV continuous infusion over 24 hours (2,400mg/m² over 46-48 hours). Repeat cycle every 2 weeks.</p>
Irinotecan and Cisplatin ^{17,24,93,d}	<p>Days 1,8: Cisplatin 25-30mg/m² IV over 1 hour, followed by: Days 1,8: Irinotecan 65mg/m² IV over 90 minutes. Repeat cycle every 3 weeks.</p>
Irinotecan and Ramucirumab (for adenocarcinoma) ^{81,89,i}	<p>Day 1: Irinotecan 150mg/m² IV over 90 minutes Day 1: Ramucirumab 8mg/kg IV over 1 hour. Repeat cycle every 2 weeks.</p>
Ramucirumab (Category 1 for EGJ adenocarcinoma; Category 2A for esophageal adenocarcinoma) ^{85,95,e,l}	<p>Day 1: Ramucirumab 8mg/kg IV over 1 hour. Repeat cycle every 2 weeks.</p>

continued

Esophageal and Esophagogastric Cancer Treatment Regimens

► Second-Line or Subsequent Systemic Therapy for Unresectable, Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated; dependent on prior therapy and PS)^e (continued)

REGIMEN	DOSING
Useful in Certain Circumstances	
Entrectinib (for <i>NTRK</i> gene fusion-positive tumors)⁹⁶⁻⁹⁸	Days 1 -28: Entrectinib 600mg orally once daily. Repeat cycle every 4 weeks.
Larotrectinib (for <i>NTRK</i> gene fusion-positive tumors)^{99,100}	Days 1 -28: Larotrectinib 100mg orally twice daily. Repeat cycle every 4 weeks.
Pembrolizumab (for MSI-H or dMMR tumors, or TMB high, >10 mutations/megabase, tumors)^{50,80-84,e,1}	Day 1: Pembrolizumab 200mg IV over 30 minutes. Repeat cycle for 3 weeks. OR Day 1: Pembrolizumab 400mg IV over 30 minutes. Repeat cycle for 6 weeks.

^a Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin.

^b Leucovorin infusion time should match the infusion time of oxaliplatin when these agents are given concurrently.

^c Premedication for hypersensitivity is required for paclitaxel: famotidine 20mg IV or orally (or equivalent H2 blocker) 30 minutes-1 hour pre-paclitaxel AND diphenhydramine 12.5-50mg IV or orally 30 minutes-1 hour pre-paclitaxel AND dexamethasone 10mg IV 30 minutes pre-paclitaxel. In the absence of infusion reactions for Doses 1-3, may consider dexamethasone 4mg IV 30 minutes pre-paclitaxel starting with Dose 4.

^d Hydration is required with supplemental electrolytes pre- and post-administration of cisplatin.

^e EGJ = esophagogastric junction; PDL1 CPS = PD-L1 expression if the combined positive score; PS = performance status; MSI-H = high levels of microsatellite instability; dMMR = deficient mismatch repair.

^f Premedication with dexamethasone for fluid retention is required. One recommended dosing strategy is: dexamethasone 8mg orally twice daily for three consecutive days starting 1 day prior to docetaxel administration.

^g Postoperative management for patients with adenocarcinomas who have not received preoperative chemoradiation or chemotherapy is based on surgical outcomes/clinical pathologic findings. For node negative R0 resection with tumor classification pT1s and pT1, surveillance is recommended. For node negative R0 resection with tumor classification pT2, surveillance is recommended or consider chemoradiation (category 2B) for select patients. Fluoropyrimidine-based chemoradiation recommended for patients with R1 or as an option for patients with R2 resection.

^h Cisplatin may not be used interchangeably with fluorouracil in regimens containing irinotecan.

ⁱ An FDA-approved trastuzumab biosimilar is an appropriate substitute for trastuzumab.

^j If no prior tumor progression while on therapy with a checkpoint inhibitor.

^k Capecitabine cannot be used interchangeably with fluorouracil in regimens containing irinotecan.

^l Ramucirumab: Premedication for infusion reactions is required. The recommended dosing is: diphenhydramine 12.5-50mg IV or orally 30 minutes pre-ramucirumab.

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