Palliative Management for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (When Local Therapy Is Not Indicated)

Unresectable locally advanced, locally recurrent, or metastatic disease

Performance Status

Karnofsky PS ≥60% or ECOG PS ≤2

Perform HER2, PD-L1, MSI by PCR/MMR by ICH testing (if not done previously) if metastatic adenocarcinoma is documented or suspected

HER2+

Trastuzumab
- Add to first-line chemotherapy for HER2-overexpressing metastatic adenocarcinoma
- Combination with fluoropyrimidine and platinum agents
- Not recommended for use with anthracyclines

All Others

First-Line Therapy
- Two-drug cytotoxic regimens are preferred because of lower toxicity
- Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation
- Oxaliplatin is generally preferred over cisplatin due to lower toxicity
- Preferred regimens
  - Fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin
  - Fluoropyrimidine (fluorouracil or capecitabine) and cisplatin

Best Supportive Care

Access the activity, “Unlocking the Benefits of Synergy Between Therapeutic Advances and Holistic Care in Gastric/GEJ Cancers: Current Evidence, Practical Guidance, and Point-of-Care Tools for Implementing a Multidisciplinary Approach to Modern Patient Care,” at PeerView.com/BBD40
### Palliative Management for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (When Local Therapy Is Not Indicated)

#### Second-Line and Subsequent Therapy

<table>
<thead>
<tr>
<th>Subsequent Therapy</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramucirumab + paclitaxel</td>
<td>1</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>1</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>1</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>1</td>
</tr>
<tr>
<td>Fluorouracil + irinotecan</td>
<td>2A</td>
</tr>
<tr>
<td>Pembrolizumab (MSI-H or dMMR tumors)</td>
<td>2A</td>
</tr>
</tbody>
</table>

#### Preferred Regimens

<table>
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<tr>
<th>Subsequent Therapy</th>
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<tbody>
<tr>
<td>Ramucirumab</td>
<td>1</td>
</tr>
<tr>
<td>Irinotecan + cisplatin</td>
<td>2A</td>
</tr>
<tr>
<td>Entrectinib or larotrectinib (NTRK gene fusion–positive tumors)</td>
<td>2A</td>
</tr>
<tr>
<td>Docetaxel + irinotecan</td>
<td>2B</td>
</tr>
</tbody>
</table>

#### Other Recommended Regimens

- Fluorouracil + irinotecan + ramucirumab | 2B |

#### Useful In Certain Circumstances

<table>
<thead>
<tr>
<th>Subsequent Therapy</th>
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<tbody>
<tr>
<td>Trifluridine + tipiracil</td>
<td>1</td>
</tr>
<tr>
<td>Pembrolizumab (MSI-H or dMMR tumors)</td>
<td>2A</td>
</tr>
<tr>
<td>Pembrolizumab (gastric adenocarcinoma with PD-L1 expression levels by CPS ≥1)</td>
<td>2A</td>
</tr>
</tbody>
</table>

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**CPS**: combined positive score; dMMR: deficient mismatch repair; ECOG: Eastern Cooperative Oncology Group; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; MMR: mismatch repair; MSI: microsatellite instability; MSI-H: MSI-high; PCR: polymerase chain reaction; PD-L1: programmed death ligand-1; PS: performance status.


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Care Starts Before Treatment

- For patients with gastric cancer, interventions undertaken to relieve symptoms and maximize quality of life will prolong survival. It is important to proactively support patients prior to starting treatment, including assessing patients’ support systems; referring to nutritionists and social workers, if needed; and providing adequate disease and treatment education.

Management of Long-Term Sequelae of Disease or Treatment

**Dumping Syndrome**

- Early:
  - Occurs within 30 minutes of meal
  - Associated with palpations, diarrhea, nausea, and cramps
- Late:
  - Occurs within 2-3 hours of a meal
  - Associated with dizziness, hunger, cold sweats, faintness
  - Encourage frequent meals scheduled throughout day
  - Consume a diet high in protein and fiber, and low in simple carbohydrates or concentrated sweets
  - Avoid fluid consumption with meals
- Severe
  - Acarbose or octreotide may help
  - Reconstructive surgery is performed if symptoms are not relieved by other therapies

**Food Related**

- Indigestion:
  - Avoid foods that increase acid production (eg, citrus juices, tomato sauces, spicy foods, caffeinated drinks) or lower gastroesophageal sphincter tone (eg, caffeine peppermint, chocolate)
  - Consider proton pump inhibitor
- Postprandial fullness or eating dysfunction:
  - Encourage small portions and more frequent eating
  - Avoid fluid intake with meals

**Weight Loss**

- Monitor weight regularly after gastrectomy to ensure stability
- Encourage more frequent feeding and avoiding fluid intake with meals
- Consider referral to dietician or nutrition services for individualized counseling
- Assess for and address contributing medical and/or psychosocial factors

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Care Strategies for Gastric Cancer

Management of Long-Term Sequelae of Disease or Treatment

Counseling Regarding Health Behaviors
- Maintain a healthy body weight
- Adopt a physically active lifestyle and avoid inactivity
- At least 30 minutes of moderate-intensity activity most days
- Modify physical activity based on treatment sequelae (ie, neuropathy)
- Consume a healthy diet with emphasis on plant sources, with modifications as needed based on treatment sequelae (ie, dumping syndrome, bowel dysfunction)
- Limit alcohol consumption
- Recommend smoking cessation as appropriate
- Additional preventive health measures and immunizations should be performed as indicated under the care of or in conjunction with a primary care physician

Vitamins and Minerals
- Vitamin B₁₂ deficiency:
  - Monitor CBC and B₁₂ levels every 3 months for up to 3 years, then every 6 months up to 5 years, then annually
  - Supplement B₁₂ as clinically indicated
- Iron deficiency:
  - Monitor CBC and iron levels at least annually
  - Supplementation with iron as clinically indicated
  - Ferric carboxymaltose injection may be beneficial for patients with iron deficiency anemia
  - For patients with total gastrectomy, avoid sustained-release or enteric-coated formulations if possible
- Review all supplements with nutritionist and oncologist (eg, vitamin B₁₂, iron, calcium, folate)
- Work with nutritionist/dietician to develop a plan for patient

Small Intestine Bacterial Overgrowth
- Consider treatment with antibiotics
  - Rifaximin 550 mg TID x 7-10 days preferred
- Consume a diet high in protein and low in carbohydrates

Bone Health
- Screen for and manage low bone density at regular intervals as per established national guidelines
- Consider vitamin D testing and replacement as clinically indicated

Anxiety
- Provide a relaxed and comfortable environment
- Encourage active participation of the patient and family in care and treatment decisions
- Allow the patient an opportunity to discuss feelings and concerns with a social worker or clergy

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**Pain**

- Assess characteristics of pain and discomfort: location, quality, frequency, duration, etc.
- Multi-modal pain management: nonopioids, opioids, topical medications, and non-pharmacological modalities

**Nausea/Vomiting**

- Antiemetics may be used to control nausea. Nausea may be related to chemotherapy side effects or the tumor itself
- Ensure that the patient is having small meals throughout the day and drinking plenty of fluids
- A bland diet and ginger can be helpful in managing nausea
- May be associated with luminal obstruction, so endoscopic or fluoroscopic evaluation should be performed to determine if obstruction is present

**Obstruction**

The primary goals of palliation for patients with malignant gastric obstruction are to reduce nausea and vomiting and, when possible, allow resumption of an oral diet.

- Alleviate or bypass obstruction
  - Endoscopy: Place enteral stent for relief of outlet obstruction or esophageal stent for EGJ/gastric cardia obstruction
  - Surgery: gastrojejunostomy or gastrectomy in select patients
  - EBRT
  - Chemotherapy
- Place percutaneous, surgical, endoscopic, or interventional radiology gastrostomy tube for gastric decompression if tumor location permits
- Reduce the risk of infectious complications by draining ascites before placing a venting gastrostomy tube
- Place feeding tubes in patients who cannot take an oral diet: gastrostomy tubes for patients with esophagogastric junction/gastric cardia obstruction and jejunal feeding tubes for patients with mid and distal gastric obstruction

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## Palliative/Best Supportive Care Strategies

### Diarrhea
- Consider anti-diarrheal agents, bulk-forming agents, and diet

### Chemotherapy-Induced Neuropathy
- Consider duloxetine for painful neuropathy only (not effective for numbness or tingling)

### Fatigue
- Encourage physical activity and energy conservation measures as tolerated
- Assess and address contributing medical and/or psychosocial factors

### Bleeding
Acute bleeding, which is common in patients with gastric cancer, may be caused by a tumor or be a consequence of therapy. Prompt endoscopic assessment is key for patients with acute bleeding.

- **Endoscopic treatment**
  - Limited efficacy studies of endoscopic therapy for bleeding in patients with gastric cancer suggest that the treatment may be effective initially, but the rate of recurrent bleeding is high
  - Widely available treatment options include injection therapy, mechanical therapy (eg, endoscopic clips), ablative therapy (eg, argon plasma coagulation), or a combination of methods
- **Interventional radiology**
  - Angiographic embolization techniques may be useful in those situations where endoscopy is not helpful or bleeding occurs
  - External beam radiation therapy
  - EBRT manages acute and chronic gastrointestinal bleeding in multiple small series

- **Chronic blood loss**
  - Although proton pump inhibitors can be prescribed to reduce bleeding risk from gastric cancer, there are no definite data supporting use
  - EBRT may be used for chronic blood loss

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EBRT: external beam radiation therapy; TID: times a day.


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Antiangiogenesis Combinations

**Phase 2**

- **Immunotherapy + Antiangiogenesis + Chemotherapy**
  - NCT04069273: SEQUEL
  - Not yet recruiting (58)
  - Pembrolizumab + ramucirumab + paclitaxel

- **Immunotherapy + Antiangiogenesis + Chemotherapy**
  - NCT03966118
  - Recruiting 59 participants
  - Avelumab + paclitaxel/ramucirumab

- **Chemotherapy + Antiangiogenesis**
  - NCT03686488
  - Recruiting 25 participants
  - Trifluridine/tipiracil + ramucirumab

**Phase 1/2**

- **Antiangiogenesis + PARP + Immunotherapy (RiME)**
  - NCT03995017
  - Recruiting 61 participants
  - Ramucirumab + rucaparib ± nivolumab

**Phase 1**

- **Immunotherapy + Antiangiogenesis**
  - NCT02572687
  - Active, not recruiting (114)
  - Ramucirumab + MEDI4736

- **PARP + Antiangiogenesis**
  - NCT03008278
  - Recruiting 49 participants
  - Olaparib + ramucirumab

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### Immunotherapy and Combinations

<table>
<thead>
<tr>
<th>Phase 3</th>
<th>Immunotherapy + Chemotherapy</th>
<th>Recruiting 650 participants&lt;br&gt;Sintilimab + oxaliplatin + capecitabine</th>
<th>Immunotherapy + Chemotherapy</th>
<th>Recruiting 1,542 participants&lt;br&gt;Pembrolizumab + chemotherapy</th>
<th>Immunotherapy + Chemotherapy</th>
<th>Recruiting 1,000 participants&lt;br&gt;Pembrolizumab + chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03745170: ORIENT-16</td>
<td>Pembrolizumab + chemotherapy&lt;br&gt;MK-3475-859/KEYNOTE-859</td>
<td>NCT03221426</td>
<td>MK-3475-859/KEYNOTE-859</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 2</th>
<th>Immunotherapy + PARP</th>
<th>Recruiting 40 participants&lt;br&gt;Paclitaxel + olaparib then durvalumab + olaparib + paclitaxel</th>
<th>Immunotherapy + PARP</th>
<th>Not yet recruiting (36)&lt;br&gt;Paclitaxel + olaparib + pembrolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03579784</td>
<td>Pembrolizumab + chemotherapy&lt;br&gt;MEDIOLA</td>
<td>NCT04209686</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 1/2</th>
<th>Immunotherapy + Monoclonal Antibody</th>
<th>Recruiting 80 participants&lt;br&gt;Bavituximab + pembrolizumab</th>
<th>Immunotherapy + Monoclonal Antibody</th>
<th>Pembrolizumab + chemotherapy&lt;br&gt;DisTinGuish</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04099641</td>
<td>Pembrolizumab + chemotherapy&lt;br&gt;DisTinGuish</td>
<td>NCT04363801:DisTinGuish</td>
<td>Pembrolizumab + chemotherapy&lt;br&gt;DisTinGuish</td>
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**HER2+ Gastric Cancer**

**Monoclonal Antibody + PD-1 Inhibitor + Chemotherapy**

- **NCT03615326: KEYNOTE-811**
  - Recruiting 732 participants
  - Trastuzumab + chemotherapy; pembrolizumab + trastuzumab + chemotherapy; placebo + trastuzumab + chemotherapy

**Monoclonal Antibody Combinations**

- **NCT04082364: MAHOGANY**
  - Recruiting 850 participants
  - Margetuximab + various combinations

**ADC**

- **NCT03556345**
  - Recruiting 125 participants
  - RC48-ADC

**ADC**

- **NCT04014075: DESTINY-Gastric02**
  - Recruiting 72 participants
  - Trastuzumab deruxtecan

**Bispecific Antibody + Chemotherapy**

- **NCT03296660: DESTINY-Gastric01**
  - Active (220), not recruiting
  - Trastuzumab deruxtecan vs placebo

**Bispecific Antibody + PD-1 Inhibitor + Chemotherapy**

- **NCT04276493**
  - Recruiting 50 participants
  - ZW25 + tislelizumab + chemotherapy

**Monoclonal Antibody + PD-1 Inhibitor**

- **NCT02689284**
  - Active (95), not recruiting
  - Margetuximab + pembrolizumab

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## Communication Principles

<table>
<thead>
<tr>
<th>Context: Sharing the “why” to reduce patient distress</th>
<th>What You Might Say</th>
</tr>
</thead>
<tbody>
<tr>
<td>• “If it’s OK, I’d like to try to explain why we are doing things this way.”&lt;br&gt;  - We expect/have a surge in people with COVID-19 here&lt;br&gt;  - The number of people needing care will soon be/is greater than resources (hospital beds, doctors, and medical supplies)&lt;br&gt;  - This has impacted how we are treating our patients with cancer during this difficult time&lt;br&gt;  - As more patients with COVID-19 come into the health system, we need to think carefully about how to:&lt;br&gt;    - Take the best care of you and optimize your cancer treatment&lt;br&gt;    - Protect you and others from getting the virus</td>
<td></td>
</tr>
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</table>

| Consideration: Highlight your process and show you’re thinking about patients’ cases | | |
| “I have talked with leaders in the cancer center and my colleagues and thought hard about your case. I/we think the best plan would be [your recommendation].” | |

| Commitment: Express your commitment to ongoing care and suggest action steps | | |
| “Part of the difficulty is the uncertainty of how long this will last. Through all of this, I will be your doctor, and we will work together to get you the best possible care.”<br>  - The best way for us to stay in touch would be [method]<br>  - The best things you can do to stay safe are [link to patient resources]<br>  - The cancer center also has more resources [link to patient resources] | |

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1. [Link to the website for more information](https://www.rogelcancercenter.org/cancer-patients-and-covid).