Activity Overview
Expert faculty review optimal treatment decisions for a patient with metastatic gastric adenocarcinoma whose disease progressed following systemic chemotherapy.

Target Audience
This activity is intended for community oncologists.
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Faculty Disclosure Statements

Johanna Bendell, MD, has indicated no real or apparent conflicts.

The peer reviewers and activity planners have no financial relationships to disclose.

Learning Objectives

Upon completion, participants should be able to:

• Individualize therapy for patients with advanced/metastatic gastric and GEJ adenocarcinoma that has progressed following initial therapy
Faculty

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Exploring Treatment Options After Disease Progression in Advanced or Metastatic Gastric/GEJ Adenocarcinoma

Case Presentation

• A 65-year-old man with a history of HTN, COPD, T2DM, and osteoarthritis presents to his PCP with anemia; he is sent for upper and lower endoscopy and on EGD is found to have a gastric mass
• Biopsy shows a poorly differentiated adenocarcinoma that is HER2 negative and MSS; PD-L1 testing shows a CPS of 5
• Scans show lung and adrenal metastases
• He is started on FOLFOX chemotherapy; he achieves SD but eventually progresses after 8 months of therapy
Systemic Therapy for Gastric Cancer: Second-Line Treatment Recommendations

• Selection depends on prior therapy, PS, and MSI/PD-L1 status
• Preferred regimens:
  – Ramucirumab + paclitaxel
  – Docetaxel
  – Paclitaxel
  – Irinotecan (+/− 5-FU)
  – Pembrolizumab (MSI-H or MMR-D tumors)

• Recent data regimens:
  – Pembrolizumab (positive data in second line for patients with CPS ≥ 10)
  – Nivolumab (positive data in ONO-4538 trial)

• Alternative regimens:
  – Ramucirumab
  – Irinotecan and cisplatin (or docetaxel)
  – Pembrolizumab (third line for patients with CPS > 1)

Randomized Second-Line Gastric Cancer Studies: Median OS Presented/Published in 2009-2014

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (mo)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramucirumab vs PBO (BSC)</td>
<td>5.2</td>
<td>0.776 (0.603-0.998)</td>
<td>.047</td>
</tr>
<tr>
<td>(N = 355)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel vs ASC (N = 168)</td>
<td>5.2</td>
<td>0.67 (0.49-0.92)</td>
<td>.01</td>
</tr>
<tr>
<td>Docetaxel or irinotecan vs BSC (N = 202)</td>
<td>5.3</td>
<td>0.657 (0.485-0.891)</td>
<td>.007</td>
</tr>
<tr>
<td>Irinotecan vs BSC (N = 40)</td>
<td>4.2</td>
<td>0.48 (0.25-0.92)</td>
<td>.012</td>
</tr>
<tr>
<td>RAM or PBO + PTX vs PTX (N = 665)</td>
<td>7.4</td>
<td>0.807 (0.678-0.962)</td>
<td>.017</td>
</tr>
</tbody>
</table>

HR, 0.807 (95% CI, 0.678-0.962) P = .017

**REGARD: OS**

- Most common adverse reactions
  - Single agent (≥ 10% and ≥ 2% higher than PBO): HTN and diarrhea
  - Ramucirumab plus paclitaxel (≥ 30% and ≥ 2% higher than PBO plus paclitaxel): fatigue, neutropenia, diarrhea, and epistaxis

<table>
<thead>
<tr>
<th>RAM</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>238</td>
</tr>
<tr>
<td>Median OS, mos (95% CI)</td>
<td>5.2 (4.4–5.7)</td>
</tr>
<tr>
<td>6-month OS</td>
<td>42%</td>
</tr>
<tr>
<td>12-month OS</td>
<td>18%</td>
</tr>
<tr>
<td>HR, 0.776 (95% CI, 0.603–0.998)</td>
<td>Log-rank (stratified) P = .047</td>
</tr>
</tbody>
</table>

![OS Graph](image1.png)

**RAINBOW: OS**

- Most common adverse reactions
  - Single agent (≥ 10% and ≥ 2% higher than PBO): HTN and diarrhea
  - Ramucirumab plus paclitaxel (≥ 30% and ≥ 2% higher than PBO plus paclitaxel): fatigue, neutropenia, diarrhea, and epistaxis

<table>
<thead>
<tr>
<th>RAM + PTX</th>
<th>PBO + PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>330</td>
</tr>
<tr>
<td>Median, mos (95% CI)</td>
<td>9.6 (8.5–10.8)</td>
</tr>
<tr>
<td>6-month OS</td>
<td>72%</td>
</tr>
<tr>
<td>12-month OS</td>
<td>40%</td>
</tr>
<tr>
<td>HR, 0.807 (95% CI, 0.678–0.962)</td>
<td>Stratified log-rank P = .017</td>
</tr>
</tbody>
</table>

![OS Graph](image2.png)
KEYNOTE-059: Phase 2 Study of Pembrolizumab for Advanced Gastric or GEJ Adenocarcinoma

• Primary endpoint: ORR per RECIST v1.1 by central review

**COHORT 1**
- PD-L1+ or PD-L1-
- Prior systemic therapies
  - n = 180

**COHORT 2**
- PD-L1+ or PD-L1-
- No prior systemic therapy
  - n = 40

**COHORT 3**
- PD-L1+ only
- No prior systemic therapy
  - n = 50

Pembrolizumab 200 mg Q3W

Pembrolizumab 200 mg + cisplatin + 5-FU, all Q3W

Pembrolizumab 200 mg Q3W

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**KEYNOTE-059 Cohort 1: Response**

<table>
<thead>
<tr>
<th>Response</th>
<th>All Patients (N = 259)</th>
<th>PD-L1 Positive (n = 148)</th>
<th>PD-L1 Negative (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>95% CI</td>
<td>%</td>
</tr>
<tr>
<td>ORR (CR + PR)</td>
<td>11.6</td>
<td>8.0-16.1</td>
<td>15.5</td>
</tr>
<tr>
<td>CR</td>
<td>2.3</td>
<td>0.9-5.0</td>
<td>2.0</td>
</tr>
<tr>
<td>PR</td>
<td>9.3</td>
<td>6.0-13.5</td>
<td>13.5</td>
</tr>
<tr>
<td>DCRb</td>
<td>33.1</td>
<td>21.7-32.9</td>
<td>33.1</td>
</tr>
<tr>
<td>Median response duration</td>
<td>Median (range) follow-up = 5.8 (0.5-21.6) months</td>
<td>16.3</td>
<td>1.6-17.3+</td>
</tr>
</tbody>
</table>

*Only confirmed responses were included; bDCR = CR + PR + SD ≥ 2 months.

KEYNOTE-061: Phase 3 Study of Pembrolizumab vs Paclitaxel (Second Line)

- Final analysis of international, randomized, open-label phase 3 trial

**Patient Population (N = 592)**
- Unresectable metastatic or locally advanced GC or GEJ adenocarcinoma
- PD following first-line platinum- and fluoropyrimidine-based regimens
- ECOG PS 0/1
- Any PD-L1 CPS in first 489 patients
- PD-L1 CPS ≥ 1 in final 103 patients

**Pembrolizumab 200 mg Q3W for up to 35 cycles (n = 296)**

**Paclitaxel 80 mg/m² on days 1, 8, and 15 of 4-week cycles (n = 296)**

- PD or intolerable toxicity, at investigator decision

**Primary endpoint: OS and PFS in CPS ≥ 1 population**
- Secondary endpoints: ORR and duration of response in CPS ≥ 1 population, safety in all treated patients

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KEYNOTE-061: OS Subgroup Analysis

- Pembrolizumab improved OS in subgroups with ECOG PS 0 and primary tumor in GEJ, as well as in post hoc analysis subgroups PD-L1 CPS ≥ 10 and MSI-H

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Protocol-Specified Subgroups</th>
<th>Post Hoc Analysis Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ECOG PS 0 (n = 180)</td>
<td>Primary tumor in GEJ (n = 135)</td>
</tr>
<tr>
<td>HR for OS (95% CI)</td>
<td>0.69 (0.49-0.97)</td>
<td>0.61 (0.41-0.90)</td>
</tr>
</tbody>
</table>

**Phase 3 KEYNOTE-181 Study (NCT02564263)**

**Key Eligibility Criteria**
- Advanced/metastatic adenocarcinoma or SCC of the esophagus or Siewert type 1 adenocarcinoma of the GEJ
- Measurable disease per RECIST v1.1
- Progression on or after first-line therapy
- ECOG PS 0-1

**Pembrolizumab**
- 200 mg IV Q3W for up to 35 cycles

**Investigator’s choice of 1 of the following:**
- Paclitaxel 80-100 mg/m² on days 1, 8, 15, Q4W
- Docetaxel 75 mg/m² Q3W
- Irinotecan 180 mg/m² Q2W

**KEYNOTE-181:**
**Pembrolizumab vs Chemotherapy in Second Line**

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>Median OS, mos</th>
<th>Pembro</th>
<th>Chemo</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 CPS ≥ 10 (n = 222)</td>
<td>9.3</td>
<td>6.7</td>
<td>0.69 (0.52-0.93)</td>
<td>.0074</td>
<td></td>
</tr>
<tr>
<td>SCC (n = 628)</td>
<td>8.2</td>
<td>7.1</td>
<td>0.78 (0.63-0.96)</td>
<td>.0095</td>
<td></td>
</tr>
<tr>
<td>ITT (n = 628)</td>
<td>7.1</td>
<td>7.1</td>
<td>0.89 (0.75-1.05)</td>
<td>.0560</td>
<td></td>
</tr>
</tbody>
</table>

- Most common adverse reactions (≥ 20% of patients): fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, and constipation
Conclusions

• How would you treat this patient?
• What if the patient had a poor PS?
• What if the patient had a CPS of 12 or MSI-H?

Instructions to Receive Credit
To receive credit, read the introductory CME material, listen to the audiocast, and complete the evaluation, attestation, and post-test, answering at least 70% of the post-test questions correctly.

Contact Information
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Abbreviations and Acronyms

S-FU = fluorouracil
AE = adverse event
AFP = alpha-fetoprotein
ASC = active symptom control
BCLC = Barcelona Clinic Liver Cancer
BID = twice a day
BSC = best supportive care
CIV = continuous intravenous infusion
COPD = chronic obstructive pulmonary disease
CPS = combined positive score
CR = complete response
CRC = colorectal cancer
CT = computed tomography
DCF = docetaxel, cisplatin, and fluorouracil
dCR = disease control rate
EASL = European Association for the Study of the Liver
EGF = epirubicin, cisplatin, and fluorouracil
ECOG = Eastern Cooperative Oncology Group
EGD = esophagogastroduodenoscopy
ESMO = European Society for Medical Oncology
FDA = Food and Drug Administration
FGFR = fibroblast growth factor receptor
FISH = fluorescence in situ hybridization
FOLFOX = folinic acid (leucovorin), fluorouracil, and irinotecan
FOLFOXIRI = folinic acid (leucovorin), fluorouracil, and oxaliplatin
GE = gastroesophageal
GEJ = gastroesophageal junction
HBV = hepatitis B virus
HCC = hepatocellular carcinoma
HCV = hepatitis C virus
HFSR = hand–foot skin reaction
HTN = hypertension
ICh = irinotecan and cisplatin
IHC = immunohistochemistry
IIE = immune-related event
ITT = intent to treat
MMR = mismatch repair
MMR-D = mismatch repair deficiency
MMR-P = mismatch repair proficiency
MSI = microsatellite instability
MSI-H = microsatellite instability high
MSI-L = microsatellite instability low
MSI = microsatellite stability
NASH = nonalcoholic steatohepatitis
NCCN = National Comprehensive Cancer Network
NE = not estimable
NGS = next generation sequencing
NR = not reached
OS = overall response rate
NS = overall survival
PBO = placebo
PCR = polymerase chain reaction
PD = progressive disease
PD-L1 = programmed death ligand-1
PFS = progression-free survival
PFPE = palmar–plantar erythrodysesthesia
PS = performance status
Q2W = every 2 weeks
Q3W = every 3 weeks
RECIST = Response Evaluation Criteria in Solid Tumors
SCC = squamous cell carcinoma
SD = stable disease
T2DM = type 2 diabetes mellitus
TMB = tumor mutation burden
TML = tumor mutation load
TTP = time to progression
WT = wild type