Ask the Investigators: Applying Emerging Clinical Research to the Care of Patients with Gastroesophageal Cancers

A Satellite Educational Symposium Held in Conjunction with the 2021 AACR Virtual Annual Meeting

Monday, April 12, 2021
6:30 PM – 7:30 PM ET

Faculty
Joseph Chao, MD
Yelena Y Janjigian, MD

Moderator
Neil Love, MD
Faculty

Joseph Chao, MD  
Associate Clinical Professor  
Department of Medical Oncology and Therapeutics Research  
GI Medical Oncology Section  
City of Hope Comprehensive Cancer Center  
Duarte, California

Yelena Y Janjigian, MD  
Associate Attending Physician  
Associate Professor, Weill Cornell Medical College  
Chief, Gastrointestinal Oncology Service  
Memorial Sloan Kettering Cancer Center  
New York, New York
Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc and Five Prime Therapeutics Inc.
Dr Love — Disclosures

Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.
<table>
<thead>
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<th>Disclosures</th>
<th>Details</th>
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<tr>
<td><strong>Advisory Committee</strong></td>
<td>Bristol-Myers Squibb Company, Daiichi Sankyo Inc, MacroGenics Inc, Merck</td>
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<td>Amgen Inc, AstraZeneca Pharmaceuticals LP, Foundation Medicine, Ono Pharmaceutical Co Ltd</td>
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<td>Brooklyn ImmunoTherapeutics, Merck</td>
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<tr>
<td><strong>Data and Safety Monitoring Board/Committee</strong></td>
<td>Yiviva</td>
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<tr>
<td><strong>Speakers Bureau</strong></td>
<td>Merck</td>
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## Dr Janjigian — Disclosures

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<td><strong>Ownership Interest (Stock Options)</strong></td>
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We Encourage Clinicians in Practice to Submit Questions

Feel free to submit questions now before the program begins and throughout the program.
Familiarizing Yourself with the Zoom Interface

How to answer poll questions

When a poll question pops up, click your answer choice from the available options. Results will be shown after everyone has answered.
Familiarizing Yourself with the Zoom Interface

Expand chat submission box

Drag the white line above the submission box up to create more space for your message.
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Increase chat font size

Press Command (for Mac) or Control (for PC) and the + symbol. You may do this as many times as you need for readability.
ONCOLOGY TODAY
WITH DR NEIL LOVE

Key Recent Data Sets in Gastrointestinal Cancers

DR PHILIP A PHILIP
KARMANOS CANCER INSTITUTE
WAYNE STATE UNIVERSITY

Listen on
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Meet The Professor
Management of Chronic Lymphocytic Leukemia

Thursday, April 15, 2021
5:00 PM – 6:00 PM ET

Faculty
John N Allan, MD

Moderator
Neil Love, MD
Dissecting the Decision: Investigator Perspectives on Key Issues in the Management of Common Cancers

**A Complimentary NCPD Live Webinar Series Hosted in Conjunction with the 46th Annual ONS Congress**

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Date</th>
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<tr>
<td>Breast Cancer</td>
<td>Tuesday, April 20, 2021</td>
<td>8:30 AM – 10:00 AM ET</td>
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<td>Non-Small Cell Lung Cancer</td>
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Ask the Expert: Clinical Investigators Provide Perspectives on the Management of Renal Cell Carcinoma

In Partnership with Project Echo® and Florida Cancer Specialists

Tuesday, May 4, 2021
5:00 PM – 6:00 PM ET

Faculty
Chung-Han Lee, MD, PhD

Moderator
Neil Love, MD
Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.
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Daniel Catenacci, MD
Associate Professor, Department of Medicine, Section of Hematology and Oncology
Director, Interdisciplinary Gastrointestinal Oncology Program
Assistant Director, Translational Research, Comprehensive Cancer Center
The University of Chicago Medical Center and Biological Sciences
Chicago, Illinois
Agenda
Cases from the Practice of Dr Catenacci

**Case 1:** A 54-year-old man with MSS metastatic GEJ adenocarcinoma – PD-L1 CPS 20, HER2-negative

**Case 2:** A 56-year-old man with localized adenocarcinoma of the esophagus – MSS, PD-L1 CPS 10

**Case 3:** A 68-year-old man with relapsed MSS adenocarcinoma of the esophagus – HER2-positive, PD-L1 CPS 0

**Case 4:** A 35-year-old woman with relapsed metastatic gastric cancer and disease progression on T-DXd

**Case 5:** A 68-year-old man with newly diagnosed metastatic GEJ cancer with an FGFR2b mutation

**Case 6:** A 66-year-old woman with metastatic squamous cell carcinoma of the esophagus – PD-L1 CPS 50

**Case 7:** A 64-year-old man with GEJ cancer and COVID-19 vaccine-associated imaging issues
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Case 7: A 64-year-old man with GEJ cancer and COVID-19 vaccine-associated imaging issues
Case Presentation – A 54-year-old man with microsatellite-stable metastatic gastroesophageal junction adenocarcinoma – PD-L1 CPS 20, HER2-negative

- Presents with dysphagia and 10-pound weight loss
  - Imaging shows liver lesions and EGD reveals mass at the GEJ
  - GEJ and liver biopsy results consistent with adenocarcinoma
- FOLFOX + pembrolizumab (400mg q6weeks) initiated
- Restaging CT demonstrates stable disease
- Therapy continued with 5-FU and pembrolizumab maintenance
  - Progressive disease at 8 months
- Patient switched to 2\textsuperscript{nd} line FOLFIRI + ramucirumab

Questions

- Do you use nivolumab or pembrolizumab for GEJ adenocarcinoma? Do you prefer cisplatin or oxaliplatin as a backbone chemotherapy?
- What dosing do you use for pembrolizumab when administering FOLFOX backbone chemotherapy?
“On March 22, 2021, the Food and Drug Administration approved pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy for patients with metastatic or locally advanced esophageal or gastroesophageal (GEJ) (tumors with epicenter 1 to 5 centimeters above the gastroesophageal junction) carcinoma who are not candidates for surgical resection or definitive chemoradiation.

Efficacy was evaluated in KEYNOTE-590 (NCT03189719), a multicenter, randomized, placebo-controlled trial that enrolled 749 patients with metastatic or locally advanced esophageal or gastroesophageal junction carcinoma who were not candidates for surgical resection or definitive chemoradiation.

The recommended pembrolizumab dose for esophageal cancer is 200 mg every 3 weeks or 400 mg every 6 weeks.”
Pembrolizumab plus Chemotherapy versus Chemotherapy as First-Line Therapy in Patients with Advanced Esophageal Cancer: The Phase 3 KEYNOTE-590 Study

Kato K et al.
ESMO 2020;Abstract LBA8_PR.
KEYNOTE-590: Overall Survival

<table>
<thead>
<tr>
<th>Median OS</th>
<th>Pembro + chemo</th>
<th>Chemo</th>
<th>HR (p-value)</th>
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<tbody>
<tr>
<td>All patients</td>
<td>12.4 mo</td>
<td>9.8 mo</td>
<td>0.73 (&lt;0.0001)</td>
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<tr>
<td>PD-L1 CPS ≥10</td>
<td>13.5 mo</td>
<td>9.4 mo</td>
<td>0.62 (&lt;0.0001)</td>
</tr>
</tbody>
</table>

Kato K et al. ESMO 2020;Abstract LBA8_PR.
KEYNOTE-590: Progression-Free Survival

ESCC

<table>
<thead>
<tr>
<th>Events</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + Chemo 80%</td>
<td>0.65</td>
<td>(0.54-0.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chemo 89%</td>
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</tbody>
</table>

12-mo rate: 24% 12-mo rate: 17% Median (95% CI): 6.3 mo (6.2-6.9) 5.8 mo (5.0-6.1)

PD-L1 CPS ≥10

<table>
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<tr>
<th>Events</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + Chemo 75%</td>
<td>0.51</td>
<td>(0.41-0.65)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chemo 88%</td>
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</table>

12-mo rate: 30% 18-mo rate: 21% Median (95% CI): 7.5 mo (6.2-8.2) 5.5 mo (4.3-6.0)

All Patients

<table>
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<th>95% CI</th>
<th>P</th>
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<td>(0.55-0.76)</td>
<td>&lt;0.0001</td>
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12-mo rate: 25% 18-mo rate: 16% Median (95% CI): 6.3 mo (6.2-6.9) 5.8 mo (5.0-6.0)

Kato K et al. ESMO 2020;Abstract LBA8_PR.
Nivolumab (Nivo) plus Chemotherapy (Chemo) versus Chemo as First-Line (1L) Treatment for Advanced Gastric Cancer/Gastroesophageal Junction Cancer (GC/GEJC)/Esophageal Adenocarcinoma (EAC): First Results of the CheckMate 649 Study

Moehler M et al.
ESMO 2020;Abstract LBA6.
CheckMate 649: Overall Survival

### Median OS

<table>
<thead>
<tr>
<th></th>
<th>Nivo + chemo (n = 641)</th>
<th>Chemo (n = 655)</th>
<th>HR (p-value)</th>
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<tr>
<td>PD-L1 CPS ≥1</td>
<td>14.0 mo</td>
<td>11.3 mo</td>
<td>0.77 (0.0001)</td>
</tr>
<tr>
<td>All treated patients</td>
<td>13.8 mo</td>
<td>11.6 mo</td>
<td>0.80 (0.0002)</td>
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Moehler M et al. ESMO 2020;Abstract LBA6.
# KEY DIFFERENCES: KEYNOTE-062 VS. CheckMate 649

<table>
<thead>
<tr>
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<th>KN062</th>
<th>CM 649</th>
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<tr>
<td><strong>Population</strong></td>
<td>CPS1, Gastric/GEJ adenocarcinoma</td>
<td>All comers, EAC/Gastric/GEJ adenocarcinoma</td>
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<tr>
<td><strong>Chemo backbone</strong></td>
<td>FP/XP</td>
<td>FOLFOX/CAPOX</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>~250/group</td>
<td>~790/group</td>
</tr>
<tr>
<td><strong>Minimum follow-up</strong></td>
<td>22 months</td>
<td>12 months</td>
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<tr>
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<th>KN062 (based on screened patients with PD-L1 status)</th>
<th>KN062 All CPS1</th>
<th>CM649 (all comers)</th>
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<tbody>
<tr>
<td><strong>CPS1</strong></td>
<td>72%</td>
<td>100%</td>
<td>82%</td>
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<tr>
<td><strong>CPS 5</strong></td>
<td>29%</td>
<td>61%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>CPS10</strong></td>
<td>17%</td>
<td>37%</td>
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Courtesy of Yelena Y Janjigian, MD
Agenda
Cases from the Practice of Dr Catenacci

**Case 1:** A 54-year-old man with MSS metastatic GEJ adenocarcinoma – PD-L1 CPS 20, HER2-negative

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**Case 6:** A 66-year-old woman with metastatic squamous cell carcinoma of the esophagus – PD-L1 CPS 50

**Case 7:** A 64-year-old man with GEJ cancer and COVID-19 vaccine-associated imaging issues
Case Presentation – A 56-year-old man with localized adenocarcinoma of the esophagus – MSS, PD-L1 CPS 10

- Presents with dysphagia and weight loss
  - EGD demonstrated large fungating mass in the distal esophagus not involving the GEJ
- Neoadjuvant carboplatin/paclitaxel initiated → surgery
- Patient then treated with adjuvant nivolumab x 6 months
  - Development of autoimmune dermatitis and hypothyroidism → treatment discontinued
- Patient continues on surveillance → NED

Questions

- Would you consider adjuvant nivolumab in this case?
- Would the PD-L1 score affect your decision (what if the PD-L1 CPS was 0)?
Regulatory and reimbursement issues aside, in which line of therapy if any would you generally recommend an anti-PD-1/PD-L1 antibody (with or without chemotherapy) for a 65-year-old patient with metastatic HER2-negative, MSS adenocarcinoma of the GEJ with a PD-L1 CPS of 5%?

1. First line
2. Second line
3. Third line
4. Beyond third line
5. I would not recommend an anti-PD-1/PD-L1 antibody
Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer (EC/GEJC) Following Neoadjuvant Chemoradiation Therapy (CRT): First Results of the CheckMate 577 Study

Kelly RJ et al
ESMO 2020;Abstract LBA9_PR
CheckMate 577: Adjuvant Nivolumab After Neoadjuvant CRT/Resection for Esophageal/GEJ Cancer

- Randomized phase III trial of adjuvant nivolumab vs placebo following neoadjuvant CRT + surgical resection* for pts with stage II/III esophageal/GEJ adenocarcinoma/SCC (N = 794)

**DFS (Primary Endpoint)**

<table>
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<tr>
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<th>Median DFS, Mos (95% CI)</th>
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<tbody>
<tr>
<td>Nivolumab (n = 532)</td>
<td>22.4 (16.6 – 34.0)</td>
</tr>
<tr>
<td>Placebo (n = 262)</td>
<td>11.0 (8.3 – 14.3)</td>
</tr>
</tbody>
</table>

HR: 0.69 (96.4% CI: 0.56 – 0.86; \( P = .0003 \))

*Residual pathologic disease ≥ ypT1 or ≥ ypN1.

Kelly RJ et al. ESMO 2020;Abstract LBA9_PR.
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Case Presentation – A 68-year-old man with relapsed MSS adenocarcinoma of the esophagus – HER2-positive, PD-L1 CPS 0

- Presents with dysphagia and weight loss
  - EGD reveals distal esophageal adenocarcinoma
  - No evidence of metastatic disease
- Neoadjuvant carboplatin/paclitaxel → surgery
- Restaging CT reveals liver lesions
- First-line FOLFOX plus trastuzumab initiated → liver and lung metastases 9 months later
- Patient switched to 2nd line FOLFIRI + ramucirumab → disease progression 15 months later
- Trastuzumab deruxtecan (T-DXd) initiated → response but discontinued after 6 months due to pneumonitis
- Patient started on 4th line T-DM1 with PD → patient enrolled in hospice

Questions
- Do you use anti-HER2 therapy perioperatively?
- Do you assess HER2 status at each progression time point to determine optimal therapy options?
What would you currently recommend as second-line therapy for a patient with metastatic **HER2-positive**, MSS adenocarcinoma of the GEJ who has experienced disease progression on first-line FOLFOX/trastuzumab?

1. Ramucirumab
2. Ramucirumab/paclitaxel
3. Continue trastuzumab and switch chemotherapy
4. Test for PD-L1 CPS and administer pembrolizumab if ≥1%
5. Test for PD-L1 CPS and administer pembrolizumab if ≥5%
6. Anti-PD-1/PD-L1 antibody
7. Trastuzumab deruxtecan
8. Other
Phase II RAMIRIS Trial of Second-Line Ramucirumab plus FOLFIRI – Patients with Advanced or Metastatic Gastroesophageal Adenocarcinoma with or without Prior Docetaxel

Lorenzen S et al. ASCO 2020;Abstract 4514.
Pivotal Randomized Phase II and III Trials of HER2-Targeted Agents for HER2-Positive Advanced Gastric or GEJ Cancer

<table>
<thead>
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<th>Trial</th>
<th>Agent</th>
<th>Line of therapy</th>
<th>Result for primary endpoint</th>
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<tbody>
<tr>
<td>ToGA</td>
<td>Trastuzumab</td>
<td>First</td>
<td>Positive</td>
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<tr>
<td>LOGiC</td>
<td>Lapatinib</td>
<td>First</td>
<td>Negative</td>
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<td>JACOB</td>
<td>Pertuzumab</td>
<td>First</td>
<td>Negative</td>
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<td>T-ACT</td>
<td>Trastuzumab</td>
<td>Second</td>
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<td>GATSBY</td>
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Mitani S et al. *Cancers* 2020; (12) 400.
“On January 15, 2021, the Food and Drug Administration approved fam-trastuzumab deruxtecan-nxki for adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

Efficacy was evaluated in a multicenter, open-label, randomized trial (DESTINY-Gastric01, NCT03329690) in patients with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma who had progressed on at least two prior regimens, including trastuzumab, a fluoropyrimidine- and a platinum-containing chemotherapy.”
Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer


DESTINY-Gastric01: Trastuzumab Deruxtecan for Previously Treated HER2-Positive Gastric Cancer

<table>
<thead>
<tr>
<th></th>
<th>T-DXd (n = 119)</th>
<th>PC (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>51%</td>
<td>14%</td>
</tr>
<tr>
<td>Confirmed ORR</td>
<td>43%</td>
<td>12%</td>
</tr>
<tr>
<td>CR</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>PR</td>
<td>34%</td>
<td>12%</td>
</tr>
</tbody>
</table>

DESTINY-Gastric01: Survival Results


Median OS: 12.5 vs 8.4 mo  
HR 0.59 (95% CI 0.39-0.88)  
p=0.01

Median PFS: 5.6 vs 3.5 mo  
HR 0.47 (95% CI 0.31-0.71)
### DESTINY-Gastric01: Select Adverse Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Trastuzumab deruxtecan (n = 125)</th>
<th></th>
<th>Physician’s choice of chemo (n = 62)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3</td>
<td>Grade 4</td>
<td>Any grade</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>63%</td>
<td>38%</td>
<td>13%</td>
<td>35%</td>
</tr>
<tr>
<td>Anemia</td>
<td>58%</td>
<td>38%</td>
<td>0</td>
<td>31%</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>39%</td>
<td>10%</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>White cell count decreased</td>
<td>38%</td>
<td>21%</td>
<td>0</td>
<td>35%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>22%</td>
<td>7%</td>
<td>0</td>
<td>24%</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>22%</td>
<td>6%</td>
<td>5%</td>
<td>3%</td>
</tr>
</tbody>
</table>

- A total of 12 patients (10%) in the trastuzumab deruxtecan group had drug-related interstitial lung disease or pneumonitis compared to 0 patients in the physician’s choice group.
- 1 drug-related death (pneumonia) occurred in the trastuzumab deruxtecan group.

Pooled Analysis of Drug-Related Interstitial Lung Disease (ILD) in 8 Single-Arm Trastuzumab Deruxtecan (T-DXd) Studies

Powell CA et al.
AACR 2021;Abstract CT167.
First-line pembrolizumab and trastuzumab in HER2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: an open-label, single-arm, phase 2 trial

Yelena Y Janjigian, Steven B Maron, Walid K Chatila, Brittanie Millang, Shweta S Chavan, Carly Alterman, Joanne F Chou, Michal F Segal, Marc Z Simmons, Parisa Mormtaz, Marina Shcherba, Geoffrey Y Ku, Alice Zervoudakis, Elizabeth S Won, David P Kelsen, David H Ilson, Rebecca J Nagy, Richard B Lanman, Ryan N Ptashkin, Mark T A Donoghue, Marinela Capanu, Barry S Taylor, David B Solit, Nikolaus Schultz, Jadyn F Hechtman
**First Line Capecitabine/Oxaliplatin/Pembrolizumab/Trastuzumab**

**Best Response**

<table>
<thead>
<tr>
<th>Response</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>32 (91%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(78%, 97%)</td>
</tr>
<tr>
<td>CR</td>
<td>6 (17)</td>
</tr>
<tr>
<td>PR</td>
<td>26 (74)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (9)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
</tr>
</tbody>
</table>

**Disease Control Rate 100%**

---

Janjigian et al Lancet Oncology 2020

Courtesy of Yelena Y Janjigian, MD
Second Line – Margetuximab/Pembrolizumab (Phase Ib/II CP-MGAH222-05 Trial)

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Patients with an objective response (%; 95% CI)</th>
<th>Disease control rate (%; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response-evaluable population</td>
<td>92</td>
<td>17 (18%; 11–28); 49 (53%; 43–64)</td>
</tr>
<tr>
<td>HER2 IHC3+ positive tissue prior to 1L</td>
<td>71</td>
<td>100% (24%; 15–36); 44 (62%; 50–73)</td>
</tr>
<tr>
<td>HER2 IHC2-positive</td>
<td>21</td>
<td>0 (24%; 8–47)</td>
</tr>
<tr>
<td>PD-L1-positive tissue prior to 1L</td>
<td>33</td>
<td>79% (33%; 18–52); 22 (67%; 48–82)</td>
</tr>
<tr>
<td>PD-L1-negative</td>
<td>41</td>
<td>3% (1%; 1–19); 19 (44%; 29–60)</td>
</tr>
<tr>
<td>HER2 IHC3+ positive and PD-L1-negative</td>
<td>25</td>
<td>11 (44%; 24–65); 18 (72%; 51–88)</td>
</tr>
<tr>
<td>HER2 IHC3+ positive and PD-L1-positive</td>
<td>34</td>
<td>3% (1%; 1–19); 19 (44%; 38–73)</td>
</tr>
<tr>
<td>HER2 IHC2-positive and PD-L1-negative</td>
<td>8</td>
<td>0 (2%; 1–19); 4 (50%; 16–84)</td>
</tr>
<tr>
<td>HER2 IHC2-positive and PD-L1-positive</td>
<td>9</td>
<td>0 (2%; 1–19); 4 (50%; 16–84)</td>
</tr>
<tr>
<td>HER2**+ positive ctDNA prior to 2L</td>
<td>48</td>
<td>88% (31%; 19–46); 31 (65%; 49–78)</td>
</tr>
<tr>
<td>HER2**+ negative</td>
<td>35</td>
<td>2% (6%; 1–19); 14 (40%; 24–58)</td>
</tr>
<tr>
<td>HER2**+ positive and PD-L1-positive</td>
<td>18</td>
<td>9 (50%; 26–74); 14 (78%; 52–94)</td>
</tr>
<tr>
<td>HER2**+ positive and PD-L1-negative and HER2 IHC3+</td>
<td>15</td>
<td>9 (60%; 32–84); 12 (80%; 52–95)</td>
</tr>
<tr>
<td>HER2**+ positive and PD-L1-negative and HER2 IHC2+</td>
<td>9</td>
<td>0 (2%; 1–19); 4 (50%; 16–84)</td>
</tr>
<tr>
<td>HER2**+ positive and PD-L1-negative and HER2 IHC2+</td>
<td>4</td>
<td>0 (2%; 1–19); 4 (50%; 16–84)</td>
</tr>
</tbody>
</table>

This table includes only confirmed responses; there were three additional unconfirmed responses. ctDNA=circulating tumour DNA, HER2**+=HER2 amplification by ctDNA, IHC=immunohistochemistry. *Confirmed complete response and confirmed partial response. **Confirmed complete response, confirmed partial response, and stable disease. #Patients who received at least one dose of margetuximab 15 mg/kg intravenously every 3 weeks and had baseline measurable disease. $One confirmed complete response was observed in the double-positive (HER2 IHC3+ and PD-L1+) subgroup.

<table>
<thead>
<tr>
<th>HER2 IHC3+ &amp; PD-L1+</th>
<th>HER2 IHC2+ &amp; PD-L1+</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 IHC3+ &amp; PD-L1+ (n=34)</td>
<td>34 (11%); 13 (11%)</td>
</tr>
<tr>
<td>HER2 IHC2+ &amp; PD-L1+ (n=8)</td>
<td>8 (2); 6 (1)</td>
</tr>
</tbody>
</table>

Overall survival (OS) at 30 months: HER2 IHC3+ & PD-L1+: 9 (31%); 7 (26%); 4 (13%); 2 (8%); HER2 IHC2+ & PD-L1+: 4 (12%); 2 (8%); 1 (4%) | 0 (0)

At risk (censored)

Costaneous of Daniel Catenacci, MD

Catenacci et al. Margetuximab plus pembrolizumab for previously treated, HER2-positive GEA (CP-MGAH22–05): a single-arm, phase 1b–2 trial. Lancet Oncology 2020
First Line – Margetuximab Plus Immune Checkpoint Inhibitor

MAHOGANY Phase 2/3 Study: Registration Path in 1L Gastric & GEJ Cancer

**Module A**
- Margetuximab + Anti-PD-1 (Chemo-free Regimen)
  - HER2+ (IHC 3+) and PD-L1+ (≥ 1% CPS)
  - Single Experimental Arm: margetuximab + MGA012
  - (n=40)
  - ORR and Tolerability
  - Go/No Go
  - (add'l patients to support potential Accelerated Approval in the US)
  - Primary Endpoint: ORR

**Module B**
- Margetuximab + Chemo + MacroGenics Checkpoint Inhibitor
  - HER2+ (IHC 3+ or IHC 2+/FISH+) regardless of PD-L1 status
  - Experimental Arm #1: margetuximab + chemo + MGA012
  - Experimental Arm #2: margetuximab + chemo + MGD013
  - Experimental Arm #3: margetuximab + chemo
  - (n=250 per arm)
  - Futility Analysis
  - Assess Safety/efficacy of Experimental Arms #1 and #2
  - BLA

* Pending chronic tax study (if regimen with MGD013 is selected).

MGA012 is an investigational anti-PD-1 monoclonal antibody
MGD013 is an investigational agent targeting both PD-1 and LAG-3
Courtesy of Daniel Catenacci, MD
Phase II Study of Avelumab and Trastuzumab with FOLFOX Chemotherapy in Previously Untreated HER2-Amplified Metastatic Gastroesophageal Adenocarcinoma

Lee MS et al.
AACR 2021;Abstract CT174.
Agenda
Cases from the Practice of Dr Catenacci

**Case 1:** A 54-year-old man with MSS metastatic GEJ adenocarcinoma – PD-L1 CPS 20,
HER2-negative

**Case 2:** A 56-year-old man with localized adenocarcinoma of the esophagus – MSS, PD-L1 CPS 10

**Case 3:** A 68-year-old man with relapsed MSS adenocarcinoma of the esophagus – HER2-positive,
PD-L1 CPS 0

**Case 4:** A 35-year-old woman with relapsed metastatic gastric cancer and disease progression on T-DXd

**Case 5:** A 68-year-old man with newly diagnosed metastatic GEJ cancer with an FGFR2b mutation

**Case 6:** A 66-year-old woman with metastatic squamous cell carcinoma of the esophagus –
PD-L1 CPS 50

**Case 7:** A 64-year-old man with GEJ cancer and COVID-19 vaccine-associated imaging issues
Case Presentation – A 35-year-old woman with relapsed metastatic gastric cancer and disease progression on T-DXd

• Presents with early satiety, dysphagia and 30 lb weight loss
  – EGD reveals mass in gastric body, adenocarcinoma HER2 amplified, MSS, CPS 1
  – Staging CE reveals liver and lung metastases
• FOLFOX/trastuzumab with symptom relief and stable disease for 9 months
  – New pleural effusions and worsening dysphagia
• Primary tumor reassessment: persistent HER2 amplification, but ctDNA and lung effusion cytology without HER2 amplification
• T-DXd initiated → lung/effusions at the time of first restaging CT
• Third line FOLFIRI plus ramucirumab

Questions
• Do you take into account the whole disease burden when assessing molecular markers to determine the next best line of therapy?
• Do you use trastuzumab deruxtecan in the third line or second line therapy?
Should a liquid biopsy be used outside the context of a clinical trial to assess HER2 status in a patient with tissue-proven overexpression?

1. Yes
2. No
# Ongoing Trials of Trastuzumab Deruxtecan (T-DXd) in HER2-Positive Gastric or GEJ Adenocarcinoma

<table>
<thead>
<tr>
<th>Trial name (Identifier)</th>
<th>Phase</th>
<th>Target accrual (N)</th>
<th>Setting</th>
<th>Treatment arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>DESTINY-Gastric04 (NCT04704934)</td>
<td>III</td>
<td>490</td>
<td>• Unresectable and/or metastatic</td>
<td>• T-DXd</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Progression on or after a trastuzumab-based regimen</td>
<td>• Ramucirumab + paclitaxel</td>
</tr>
<tr>
<td>DESTINY-Gastric03 (NCT04379596)</td>
<td>II</td>
<td>220</td>
<td>• Locally advanced, unresectable or metastatic</td>
<td>Part 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Progression on or after at least 1 prior trastuzumab-based regimen</td>
<td>• T-DXd + 5-FU ± oxaliplatin (Ox)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– Part 1</td>
<td>• T-DXd + Cape ± Ox</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– Part 2</td>
<td>• T-DXd + durvalumab ± 5-FU or Cape</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Previously untreated dx – Part 2</td>
<td>Part 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Trastuzumab + 5-FU or Cape + Ox or Cisplatin</td>
<td>• T-DXd monotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• T-DXd + 5-FU or Cape ± Ox</td>
<td>• T-DXd + 5-FU or Cape + durvalumab</td>
</tr>
</tbody>
</table>

Janjigian YY et al. ESMO 2020;Abstract 1500TiP; Clinicaltrials.gov; Accessed January 2021.
MOUNTAINEER-02: Phase II/III Study of Tucatinib, Trastuzumab, Ramucirumab, and Paclitaxel in Previously Treated HER2+ Gastric or Gastroesophageal Junction Adenocarcinoma — Trial in Progress

Strickler JH et al.
Gastrointestinal Cancers Symposium 2021;Abstract TPS252.
**Study Design**

**Multi-cohort, Open-label Phase 2**
- HER2+ by NGS of ctDNA or IHC/ISH of tissue
- Paclitaxel Dose Optimization
  - N=6–12
  - Pac 60 or 80 mg/m² + TUC + Tras + Ram
- HER2+ by ctDNA
- HER2- by ctDNA, HER2+ by tissue

**Cohort 2A**
- N=24–30
- TUC + Tras + Ram + Pac

**Cohort 2B (Exploratory)**
- N=24–30
- TUC + Tras + Ram + Pac

**Double Blind, Placebo-controlled Phase 3**
- HER2+ by ctDNA
- Randomize 8:8:1
  - **Arm 3A (Test, N=235)**
    - TUC + Tras + Ram + Pac
  - **Arm 3B (Control, N=235)**
    - TUC placebo + Tras placebo + Ram + Pac
  - **Arm 3C (N=30)**
    - TUC + Tras placebo + Ram + Pac

* Formal statistical comparisons to be made between Arms 3A and 3B
* Randomization stratified by Asia vs Rest of World, Time to Progression, Prior Gastrectomy

* The SMC may recommend proceeding to Phase 3 if the regimen is safe and tolerable and an ORR ≥36% is observed in all response-evaluable patients treated at the Pac RD who have HER2+ disease by NGS assay of ctDNA.

Agenda

Cases from the Practice of Dr Catenacci

Case 1: A 54-year-old man with MSS metastatic GEJ adenocarcinoma – PD-L1 CPS 20, HER2-negative

Case 2: A 56-year-old man with localized adenocarcinoma of the esophagus – MSS, PD-L1 CPS 10

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Case 5: A 68-year-old man with newly diagnosed metastatic GEJ cancer with an FGFR2b mutation

Case 6: A 66-year-old woman with metastatic squamous cell carcinoma of the esophagus – PD-L1 CPS 50

Case 7: A 64-year-old man with GEJ cancer and COVID-19 vaccine-associated imaging issues
Case Presentation – A 68-year-old man with newly diagnosed metastatic GEJ cancer with an FGFR2b mutation

- Presents with dysphagia
  - EGD demonstrates mass in distal esophagus/GEJ extending into the gastric cardia
  - Biopsy confirmed adenocarcinoma
- MSS | HER2 neg | PD-L1 CPS 2 | FGFR2 amplified and overexpressing
- FOLFOX/bemarituzumab initiated \(\rightarrow\) excellent response
- Oxaliplatin stopped after 8 cycles due to neuropathy
- Patient continues on 5-FU/bemarituzumab \(\rightarrow\) stable disease ~ 30 months

Questions
- Do you routinely assess for FGFR2 amplification/overexpression, and if so, how?
- Do you routinely stop oxaliplatin after 6-8 doses to limit cumulative neuropathy or do you continue treatment until PD/neuropathy before stopping it?
In general, FGFR2 status should be assessed in all patients with metastatic gastroesophageal cancer.

1. Agree, by IHC
2. Agree, by RTPCR
3. Agree, by either IHC or RTPCR
4. Disagree
A double-blind randomized study of bemarituzumab (bema) plus mFOLFOX6 versus placebo plus mFOLFOX6 as first-line treatment for advanced gastric/gastroesophageal junction cancer (FIGHT)

Zev A Wainberg, Peter Enzinger, Yoon-Koo Kang, Kensai Yamaguchi, Shukui Qin, Keun-Wook Lee, Sang Cheul Oh, Jin Li, Haci Mehmet Turk, Alexandra Teixeira, Giovanni Gerardo Cardellino, Rachel Guardeno Sanchez, Siddhartha Mitra, Yingsi Yang, Helen Collins, Daniel V Catenacci

1University of California, Los Angeles, USA, 2Dana Farber Cancer Institute, Boston, USA, 3Asan Medical Center, Seoul, South Korea, 4The Cancer Institute Hospital of JFCR, Koto-Ku, Tokyo, Japan, 5181 Hospital Nanjing University of Chinese Medicine, Nanjing, China, 6Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, S.Korea, 7Korea University Guro Hospital, Seoul, South Korea, 8Shanghai East Hospital, Shanghai, China, 9Bezmialem Vakif Universitesi Tip Fakultesi Hastanesi, Fatih, Turkey, 10Hospital Senhora Da Oliveira, Guimarães, Portugal, 11Dipartimento di Oncologia, Azienda Ospedaliero Universitaria, Udine, Italy, 12Institut Catala d Oncologia Girona, Spain, 13Five Prime Therapeutics, South San Francisco, USA, 14University of Chicago, Chicago, USA

Late Breaking Abstract (LBA160)

ASCO Gastrointestinal Cancer Symposium 2021

Presented By Zev Wainberg at 2021 Gastrointestinal Cancers Symposium
Bemarituzumab is an IgG1 antibody specific for the FGFR2b Receptor

Presented By Zev Wainberg at 2021 Gastrointestinal Cancers Symposium

- Confirmed ORR = 18% (n=28)\(^1\)
- No dose-limiting toxicities
- Corneal adverse events in 3/28 patients
- Recommended Phase 2 dose: 15mg/kg Q2W with a single 7.5mg/kg dose on Cycle 1 Day 8\(^2\)

---

1 Catenacci, et al: JCO 2020
2 Tejani, et al: ASCO GI 2019
FIGHT Trial Design

Key Eligibility Criteria
- No prior therapy for unresectable locally advanced or metastatic gastric/GEJ adenocarcinoma
- RECIST v1.1 evaluable disease
- FGFR2b overexpression by IHC and/or FGFR2 gene amplification by ctDNA
- ECOG 0/1
- HER2 not positive
- May receive 1 dose of mFOLFOX6

Stratification Factors
- Geographic region
- Single dose of mFOLFOX6 during screening
- Prior adjuvant or neo-adjuvant chemotherapy

Double blind, placebo controlled

Bema + mFOLFOX6 (n = 77)

Placebo + mFOLFOX6 (n = 78)

Treatment Q2W

Primary endpoint
- Investigator-Assessed Progression-Free Survival

Secondary endpoints
- Overall Survival
- Response Rate

Statistical Plan
Trial initially designed as registrational Phase 3 (n=548) with 2-sided α 0.05 Amended after enrolling n = 155 to a proof-of-concept Phase 2 with pre-specified statistical assumptions of:
- Hierarchical sequential testing: PFS, then OS/ORR
- ≥84 events to demonstrate benefit at a HR≤0.76 for PFS at 2-sided α of 0.2

1 Central testing: Immunohistochemical stain (Ventana): cut-off any 2+/3+; circulating tumor DNA (PGDx): cut-off 1.5X
2 15mg/kg Q2W with a single 7.5mg/kg dose on Cycle 1 Day

Presented By Zev Wainberg at 2021 Gastrointestinal Cancers Symposium
Progression-Free Survival and Overall Survival: Intent to Treat

**PFS Primary Endpoint**

- **Median PFS, mo (95% CI)**: Bema (N = 77) 9.5 (7.3, 12.9); Placebo (N = 78) 7.4 (5.8, 8.4)
- **HR (95% CI)**: Bema 0.68 (0.44, 1.04)

**OS Key Secondary Endpoint**

- **Median OS, mo (95% CI)**: Bema (N = 77) NR (13.8, NR); Placebo (N = 78) 12.9 (9.1, 15.0)
- **HR (95% CI)**: Bema 0.58 (0.35, 0.95)

Presented By Zev Wainberg at 2021 Gastrointestinal Cancers Symposium
Best % Change in Target Lesions from Baseline

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Bema + mFOLFOX6</th>
<th>Placebo + mFOLFOX6</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (ITT) n/N, %</td>
<td>36/77, 47%</td>
<td>26/78, 33%</td>
</tr>
<tr>
<td>ORR (Measurable Disease at Baseline) n/N, %</td>
<td>35/66, 53%</td>
<td>24/60, 40%</td>
</tr>
<tr>
<td>Best % change in tumor size, mean (Std)</td>
<td>-41.7 (33.76)</td>
<td>-29.9 (30.49)</td>
</tr>
<tr>
<td>Median TTR (mon.), (range)</td>
<td>1.84 (1.7, 7.6)</td>
<td>1.87 (1.6, 7.3)</td>
</tr>
<tr>
<td>Median DOR (mon.), (95% CI)</td>
<td>12.2 (5.5, 15.6)</td>
<td>7.1 (4.3, 11.7)</td>
</tr>
</tbody>
</table>

Only subjects with measurable disease at baseline and at least 1 evaluable scan postbaseline are included in the waterfall plot.

DOR = Duration of response; TTR = Time to response

\(^a\) estimated among subjects with measurable disease at baseline

Presented By Zev Wainberg at 2021 Gastrointestinal Cancers Symposium
## FIGHT: Corneal-Related Adverse Events

Trial required corneal evaluation at baseline and every 8 weeks until the end of treatment\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Bema (N = 76)</th>
<th>Placebo (N = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal Adverse Events (SMQ)(^2) All Grade(^3)</td>
<td>51 (67.1%)</td>
<td>8 (10.4%)</td>
</tr>
<tr>
<td>Corneal Adverse Events (SMQ) Grade 3(^4)</td>
<td>18 (23.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Median time to onset to any grade, weeks (range)</td>
<td>16.1 (0.1, 41.0)</td>
<td>11.6 (6.0, 29.0)</td>
</tr>
<tr>
<td>Corneal AE leading to bema/placebo discontinuation(^5)</td>
<td>20 (26.3%)</td>
<td>0</td>
</tr>
<tr>
<td>AE resolved</td>
<td>12 (60.0%)</td>
<td>0</td>
</tr>
<tr>
<td>AE not resolved as of 23 Sept 2020</td>
<td>8 (40.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Median time to resolution, weeks (95%CI)</td>
<td>27.0 (18.9, NR)</td>
<td>NA</td>
</tr>
</tbody>
</table>

---

1. If any event reported, examinations were to continue every 8W until resolution, even if drug discontinued
2. SMQ = Standardised MedDRA Query
3. Most common: dry eye (26.3%), keratitis (15.8%), punctate keratitis (14.5%), vision blurred (15.0%), corneal epithelium defect (10.5%)
4. No ≥ grade 4 event reported
5. Most common: dry eye (n=4), keratitis (n=4), corneal disorder (n=2), eye disorder (n=2) limbal stem cell deficiency (n=2), punctate keratitis (n=2)

Courtesy of Daniel Catenacci, MD
Agenda
Cases from the Practice of Dr Catenacci

Case 1: A 54-year-old man with MSS metastatic GEJ adenocarcinoma – PD-L1 CPS 20, HER2-negative

Case 2: A 56-year-old man with localized adenocarcinoma of the esophagus – MSS, PD-L1 CPS 10

Case 3: A 68-year-old man with relapsed MSS adenocarcinoma of the esophagus – HER2-positive, PD-L1 CPS 0

Case 4: A 35-year-old woman with relapsed metastatic gastric cancer and disease progression on T-DXd

Case 5: A 68-year-old man with newly diagnosed metastatic GEJ cancer with an FGFR2b mutation

Case 6: A 66-year-old woman with metastatic squamous cell carcinoma of the esophagus – PD-L1 CPS 50

Case 7: A 64-year-old man with GEJ cancer and COVID-19 vaccine-associated imaging issues
Case Presentation – A 66-year-old woman with metastatic squamous cell carcinoma of the esophagus – PD-L1 CPS 50

• Presents with dysphagia, weight loss and chronic cough
  – EGD reveals mass at the proximal/mid esophagus consistent with squamous cell esophageal cancer
  – Staging CT: Liver and bone metastases, signs of chronic aspiration superimposed on emphysematous changes
• FOLFOX + pembrolizumab (400mg q6weeks) initiated → Stable disease
• Persistent dysphagia
  – G-tube placed; palliative carboplatin/paclitaxel/RT initiated

Questions
• Do you consider definitive CRT in patients with Stage IV esophageal SCC?
• Would you resume pembrolizumab after completion of definitive CRT and what is the rationale for your decision?
Regulatory and reimbursement issues aside, in which line of therapy would you generally recommend an anti-PD-1/PD-L1 antibody (with or without chemotherapy) for a 65-year-old patient with metastatic HER2-negative, MSS squamous cell carcinoma of the esophagus with a PD-L1 CPS of 5%?

1. First line
2. Second line
3. Third line
4. Beyond third line
5. I would not recommend an anti-PD-1/PD-L1 antibody
Agenda

Case 1: A 54-year-old man with MSS metastatic GEJ adenocarcinoma – PD-L1 CPS 20, HER2-negative

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Case Presentation – A 64-year-old man with GEJ cancer and COVID-19 vaccine-associated imaging issues

• Presents with localized GEJ cancer, with positive perigastric nodes
• Positive subpectoral and axillary lymph nodes identified – “hot on PET”
• At multidisciplinary tumor board, surgeon questions whether this is Stage IV disease
  – Should therapy be withheld?
• Subsequently learned that the patient received a COVID-19 vaccine on the same side as the subpectoral and axillary nodes
Appendix
Pembrolizumab was noninferior to chemotherapy for OS in patients with CPS ≥1, and a clinically meaningful improvement in OS was reported with pembro vs chemo for patients with CPS ≥10.

Pembrolizumab + chemotherapy did not show superior OS for patients with CPS ≥1 or CPS ≥10, and the combination did not show superior PFS for patients with CPS ≥1.

Shitara K et al. JAMA Oncol 2020;6(10):1571-80.
**Phase 3 KEYNOTE-181 Study**  
(NCT02564263)

**Key Eligibility Criteria**
- Advanced/metastatic adenocarcinoma or squamous-cell carcinoma 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

**Stratification by**
- Histology: squamous-cell carcinoma/adenocarcinoma
- Region: Asia/Rest-of-world

**Primary end points**
- OS in patients
  - In the ITT group
  - With SCC
  - Whose tumor had a PD-L1 CPS ≥10

**Secondary end points**
- PFS
- ORR
- Safety

**Exploratory end points**
- HRQoL in patients whose tumor had a PD-L1 CPS ≥10

**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

Presented By Takashi Kojima at 2019 Gastrointestinal Cancer Symposium and Sung-Bae Kim at 2019 ESMO Asia Congress  
Courtesy of Zev Wainberg, MD, MSc
KEYNOTE-181: Overall Survival in the Global Population

PD-L1 CPS ≥10 (n = 222)

<table>
<thead>
<tr>
<th></th>
<th>Events, %</th>
<th>Median, mo (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>107</td>
<td>84</td>
<td>9.3 (6.6-12.5)</td>
</tr>
<tr>
<td>Chemo</td>
<td>115</td>
<td>95</td>
<td>6.7 (5.1-8.2)</td>
</tr>
</tbody>
</table>

SCC (n = 403)

<table>
<thead>
<tr>
<th></th>
<th>Events, %</th>
<th>Median, mo (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>199</td>
<td>86</td>
<td>8.2 (6.7-10.0)</td>
</tr>
<tr>
<td>Chemo</td>
<td>204</td>
<td>93</td>
<td>7.1 (6.1-8.2)</td>
</tr>
</tbody>
</table>

ITT (N = 628)

<table>
<thead>
<tr>
<th></th>
<th>Events, %</th>
<th>Median, mo (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>314</td>
<td>88</td>
<td>7.1 (6.2-8.1)</td>
</tr>
<tr>
<td>Chemo</td>
<td>314</td>
<td>94</td>
<td>7.1 (6.3-8.0)</td>
</tr>
</tbody>
</table>

Data cutoff: February 13, 2019; these data represent an additional 4 months of follow up data from the October 15, 2018 cutoff.

Courtesy of Zev Wainberg, MD, MSc
KEYNOTE-181: Overall Survival (PD-L1 CPS ≥10) for Patients with Squamous Cell Carcinoma

- ORR higher with pembrolizumab than with chemotherapy for patients with CPS ≥10 (21.5% vs 6.1%)
- Lower frequency of Grade 3-5 treatment-related adverse events with pembrolizumab than with chemotherapy (18.2% vs 40.9%); no new safety signals observed


<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>Median, mo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>0.69</td>
<td>9.3</td>
<td>0.0074</td>
</tr>
<tr>
<td>Chemo</td>
<td>—</td>
<td>6.7</td>
<td></td>
</tr>
</tbody>
</table>

OS, %  
- 43%  
- 26%  
- 20%  
- 11%
Nivolumab plus Chemotherapy versus Chemotherapy Alone in Patients with Previously Untreated Advanced or Recurrent Gastric/Gastroesophageal Junction (G/GEJ) Cancer: ATTRACTION-4 (ONO-4538-37) Study

Boku N et al.
ESMO 2020;Abstract LBA7_PR.
ATTRACTION-4: Progression-Free Survival (Interim Analysis)

- PFS was continuously longer in NIVO + Chemo than in Chemo at the final analysis (NIVO+Chemo vs. Chemo: HR 0.70; mPFS 10.9 vs. 8.4 mo)

Courtesy of Yelena Y Janjigian, MD
ATTRACTION-4: Final Analysis of OS

<table>
<thead>
<tr>
<th></th>
<th>Nivo + chemo (n = 362)</th>
<th>Placebo + chemo (n = 362)</th>
<th>HR (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>17.45 mo</td>
<td>17.15 mo</td>
<td>0.90 (0.257)</td>
</tr>
</tbody>
</table>

Boku N et al. ESMO 2020;Abstract LBA7_PR.
Trifluridine/Tipiracil Outcomes in Third or Later Lines versus Placebo in Metastatic Gastric Cancer Treatment: An Exploratory Subgroup Analysis from the TAGS Study

Tabernero J et al.
Gastrointestinal Cancers Symposium 2021;Abstract 229.
TAGS Exploratory Subgroup Analysis: Median OS in the ITT Population

Rainbow-Asia: A Randomized, Multicenter, Double-Blind, Phase III Study of Ramucirumab plus Paclitaxel versus Placebo plus Paclitaxel in the Treatment of Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma Following Disease Progression on First-Line Chemotherapy with Platinum and Fluoropyrimidine

Xu R et al.  
Gastrointestinal Cancers Symposium 2021;Abstract 199.
**STUDY DESIGN**

- Histopathologically or cytologically confirmed diagnosis of gastric or GEJ adenocarcinoma
- Have metastatic disease or locally advanced, unresectable disease
- Have at least 1 measurable lesion
- Progression on or within 4 months after first-line therapy with platinum and fluoropyrimidine with or without anthracycline
- ECOG PS ≤ 1

**Randomization**

- **Ramucirumab 8 mg/kg IV D1&15 + Paclitaxel 80 mg/m² IV D1, 8, 15**
  - 28-day cycle
  - N = 294

- **Placebo 8 mg/kg IV D1&15 + Paclitaxel 80 mg/m² IV D1, 8, 15**
  - 28-day cycle
  - N = 146

**Co-primary endpoints:**
- PFS and OS

**Secondary endpoints:**
- ORR, DOR, Safety, etc.

**Stratification factors:**
- ECOG PS (0 vs. 1)
- Peritoneal metastasis (yes vs. no)

**N=440**

**Statistical consideration:** 336 deaths will provide at least 80% probability to assure that the treatment effect observed in this study is consistent with the global study.

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**Abbreviations:**
- DOR = duration of response
- ECOG PS = Eastern Cooperative Oncology Group performance status
- GEJ = gastroesophageal junction
- IV = intravenous
- N = number of patients
- PFS = progression-free survival
- ORR = objective response rate
- OS = overall survival
- TTP = time to progression
KEY RESULT

Efficacy Co-Primary Endpoints

**Progression-Free Survival (ITT)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients/Events</th>
<th>Median (months) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramucirumab + Paclitaxel</td>
<td>294/227</td>
<td>4.14 (3.71, 4.30)</td>
</tr>
<tr>
<td>Placebo + Paclitaxel</td>
<td>146/130</td>
<td>3.15 (2.83, 4.14)</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.765 (0.613, 0.955)
Stratified log-rank p-value = 0.0184

**Overall Survival (ITT)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients/Events</th>
<th>Median (months) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramucirumab + Paclitaxel</td>
<td>294/242</td>
<td>8.71 (7.98, 9.49)</td>
</tr>
<tr>
<td>Placebo + Paclitaxel</td>
<td>146/121</td>
<td>7.92 (6.31, 9.10)</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.963 (0.771, 1.203)
Stratified log-rank p-value = 0.7426

Xu R et al. Gastrointestinal Cancers Symposium 2021;Abstract 199.
Three-Year Follow-Up of ATTRACTION-3: A Phase III Study of Nivolumab (Nivo) in Patients with Advanced Esophageal Squamous Cell Carcinoma (ESCC) That Is Refractory or Intolerant to Previous Chemotherapy

Chin K et al.
Gastrointestinal Cancers Symposium 2021;Abstract 204.
ATTRACTION-3: Nivolumab for Esophageal Squamous Cell Carcinoma (ESCC)

Key eligibility criteria
- Unresectable advanced or recurrent ESCC
- Refractory to or intolerant of 1 prior fluoropyrimidine/platinum-based therapy
- ECOG performance status 0 or 1

Stratification:
- Region
- No. of organs with metastases
- PD-L1 expression

Primary endpoint:
- OS

Other key endpoints:
- PFS, ORR, DCR, TTR, DOR, HRQoL, and safety

Nivolumab 240 mg IV Q2W

Docetaxel 75 mg/m² IV Q3W or paclitaxel 100 mg/m² IV QW ✖️ 6 weeks, then 1 week off

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Chemotherapy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>19%</td>
<td>22%</td>
<td>0.63</td>
</tr>
<tr>
<td>Disease Control Rate</td>
<td>37%</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>Median Time to Response</td>
<td>2.6 months</td>
<td>1.5 months</td>
<td></td>
</tr>
<tr>
<td>Duration of Response</td>
<td>6.9 months</td>
<td>3.9 months</td>
<td></td>
</tr>
<tr>
<td>Treatment-Related Adverse Events</td>
<td>66%</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>Dose delays due to Adverse Events</td>
<td>39%</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

Cho BC et al ESMO 2019 Annual Congress and Kato K et al Lancet Oncology 2019

Courtesy of Zev Wainberg, MD, MSc
ATTRACTION-3: Overall Survival (3-Year Follow-Up)

- No new safety signal was identified with 3 years follow-up and no major late-onset TRAEs were observed

Chin K et al. Gastrointestinal Cancers Symposium 2021;Abstract 204.
ATTRACTION-3: OS Landmark Analysis at 4 Months by Best Overall Response – Stable Disease

Chin K et al. Gastrointestinal Cancers Symposium 2021;Abstract 204.
ATTRACTION-3: OS Landmark Analysis at 4 Months by Best Overall Response – Progressive Disease

Chin K et al. Gastrointestinal Cancers Symposium 2021;Abstract 204.
Nivolumab in advanced esophageal squamous cell carcinoma (ATTRACTION-1/ONO-4538-07): Minimum of 5-year follow-up

Ken Kato1, Yuichiro Doki2, Takashi Ura3, Yasuo Hamamoto4, Takashi Kojima5, Takahiro Tsushima6, Shuichi Hironaka7, Hiroki Hara8, Taroh Satoh9, Satoru Iwasa1, Kei Muro10, Hiroyumi Yasui6, Keiko Minashi11, Kensei Yamaguchi12, Atsushi Ohtsu13, Yuko Kitagawa14

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ATTRACTION-1: Efficacy

• At a minimum follow-up of five years, the median duration of OS and PFS were 10.8 and 1.5 months, respectively.

**Overall Survival**

Median OS, months (95% CI): 10.8 (7.4–13.9)

**Progression-free survival**

Median PFS, months (95% CI): 1.5 (1.4–2.8)

N = 64, one patient had multiple primary cancers and was excluded from the analysis of primary and secondary endpoints
OS, overall survival; PFS, progression-free survival

Presented By Ken Kato at 2021 Gastrointestinal Cancers Symposium
Conclusions

- Nivolumab demonstrated durable efficacy in patients with advanced ESCC based on a minimum of 5-year update of ATTRACTION-1 study.
- No new safety signals with nivolumab were identified.
- Long-term survivors tended to show the deeper response (e.g., complete response) of nivolumab in this study.
Meet The Professor
Management of Chronic Lymphocytic Leukemia

Thursday, April 15, 2021
5:00 PM – 6:00 PM ET

Faculty
John N Allan, MD

Moderator
Neil Love, MD
Thank you for joining us!

CME credit information will be emailed to each participant within 3 business days.