Metastatic Gastroesophageal Cancers: Current and Emerging Treatment Options

Jaffer Ajani, MD
The University of Texas MD Anderson Cancer Center
Audience Polling Results

This patient has a HER2 positive GAC. You will add trastuzumab to which of the following combinations?

1. Fluopyridimine plus a platinum compound
2. ECF or ECF modification
3. DCF or DCF medication
4. Irinotecan-based therapy

51% 14% 19% 16%
Audience Polling Results

This patient has a HER2 negative GAC. You will start him on which of the following?

1. Cisplatin + 5 FU
2. ECF or medication
3. Oxaliplatin + Fluopyrimidine
4. FOLFIRI
5. Add ramucirumab to any of the above

Based on data from SEER 18 2005-2011. Gray figures represent those who have died from stomach cancer. Green figures represent those who have survived 5 years or more.
GAC

At a Glance

<table>
<thead>
<tr>
<th>Estimated New Cases in 2015</th>
<th>24,590</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of All New Cancer Cases</td>
<td>1.5%</td>
</tr>
<tr>
<td>Estimated Deaths in 2015</td>
<td>10,720</td>
</tr>
<tr>
<td>% of All Cancer Deaths</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Median Survival for all comers: 9-10 months

Most patients are very Symptomatic and nutritionally deficient

- 2-year survival = 30%
- 3-year survival = 20%
- 5-year survival = <3%


Metastatic GAC

Median Survival for all comers: 9-10 months

Most patients are very Symptomatic and nutritionally deficient

- 2-year survival = 30%
- 3-year survival = 20%
- 5-year survival = <3%
**FOLLOW-UP**

- Karnofsky performance score ≥60%
- ECOG performance score ≤2

Unresectable locally advanced, Locally recurrent or metastatic disease

**PERFORMANCE STATUS**

- Karnofsky performance score <60%
- ECOG performance score ≥3

**PALLIATIVE MANAGEMENT**

- Systemic therapy or Clinical trial or Palliative/Best supportive care
- Palliative/Best supportive care

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**PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING**

**Assessment of Overexpression of HER2-neu in Gastric Cancer**

For patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach or esophagogastric junction for whom trastuzumab therapy is being considered, assessment for tumor HER2-neu overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization method is recommended. The following criteria used in the ToGA trial are recommended:
### TABLE 3

**PRINCIPLES OF PATHOLOGIC REVIEW AND HER2-NEU TESTING**

<table>
<thead>
<tr>
<th>Surgical Specimen Expression Pattern, Immunohistochemistry</th>
<th>Biopsy Specimen Expression Pattern, Immunohistochemistry</th>
<th>HER2-neu Overexpression Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No reactivity or membranous reactivity in &lt;10% of cancer cells</td>
<td>No reactivity or no membranous reactivity in any cancer cell</td>
</tr>
<tr>
<td>1+</td>
<td>Faint or barely perceptible membranous reactivity in ≥10% of cancer cells; cells are reactive only in part of their membrane</td>
<td>Cancer cell cluster with a faint or barely perceptible membranous reactivity irrespective of percentage of cancer cells positive</td>
</tr>
<tr>
<td>2+</td>
<td>Weak to moderate complete, basolateral or lateral membranous reactivity in ≥10% of tumor cells</td>
<td>Cancer cell cluster with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of tumor cells positive</td>
</tr>
<tr>
<td>3+</td>
<td>Strong complete, basolateral or lateral membranous reactivity in ≥10% of cancer cells</td>
<td>Cluster of five or more cancer cells with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive</td>
</tr>
</tbody>
</table>

*The NCCN Guidelines panel recommends that cases showing less than 3+ overexpression of HER2-neu by immunohistochemistry should be additionally examined by FISH or other in situ hybridization methods. Cases with 3+ overexpression by IHC or FISH-positive (HER2/CSP/17 ratio ≥2) are considered positive.  

### Table 13

**Study 7: Overall Survival in ITT Population**

<table>
<thead>
<tr>
<th></th>
<th>FC Arm N=296</th>
<th>FC + H Arm N=298</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definitive (Second Interim) Overall Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. Deaths (%)</td>
<td>184 (62.2%)</td>
<td>167 (56.0%)</td>
</tr>
<tr>
<td>Median</td>
<td>11.0</td>
<td>13.5</td>
</tr>
<tr>
<td>95% CI (mos.)</td>
<td>(9.4, 12.5)</td>
<td>(11.7, 15.7)</td>
</tr>
<tr>
<td><strong>Hazard Ratio</strong></td>
<td>0.73</td>
<td>0.60, 0.91</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.038</td>
<td></td>
</tr>
<tr>
<td><strong>Updated Overall Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. Deaths (%)</td>
<td>227 (76.7%)</td>
<td>221 (74.2%)</td>
</tr>
<tr>
<td>Median</td>
<td>11.7</td>
<td>13.1</td>
</tr>
<tr>
<td>95% CI (mos.)</td>
<td>(10.3, 13.0)</td>
<td>(11.9, 15.1)</td>
</tr>
<tr>
<td><strong>Hazard Ratio</strong></td>
<td>0.80</td>
<td>0.67, 0.97</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Comparing with the nominal significance level of 0.0193.

Trastuzumab Prescribing information.
**Updated Trastuzumab Survival Benefit**

**Product-Limit Survival Estimates**
With Number of Subjects at Risk

![Graph showing survival probability over duration of survival for different treatment regimens](image)

Trastuzumab Prescribing Information.

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**NCCN Guidelines Version 1.2016**
**Gastric Cancer**

**PRINCIPLES OF SYSTEMIC THERAPY**

- Systemic therapy regimens recommended for advanced esophageal and esophagogastric junction (EGJ) adenocarcinoma, squamous cell carcinoma of the esophagus, and gastric adenocarcinoma may be used interchangeably (except as indicated).
- Regimens should be chosen in the context of performance status (PS), medical comorbidities, and toxicity profile.
- Trastuzumab should be added to chemotherapy for HER2-neu overexpressing metastatic adenocarcinoma.
- Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.
- Modifications of category 1 regimen or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting a more favorable toxicity profile without compromising efficacy.
- Doses and schedules for any regimen that is not derived from category 1 evidence are a suggestion, and are subject to appropriate modifications depending on the circumstances.

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**PRINCIPLES OF SYSTEMIC THERAPY**

- Alternate combinations and schedules of cytotoxics based on the availability of the agents, practice preferences, and contraindications are permitted.
- Infusional fluorouracil and capecitabine may be used interchangeably without compromising efficacy (except as indicated). Infusion is the preferred route compared with bolus fluorouracil.
- Cisplatin and oxaliplatin may be used interchangeably depending on toxicity profile.
- Perioperative chemotherapy, or postoperative chemotherapy plus chemoradiation is the preferred approach for localized gastric cancer.
- Postoperative chemotherapy is recommended following primary D2 lymph node dissection. (See Principles of Surgery [GAST-C])
- Induction chemotherapy may be appropriate as clinically indicated.
- In the adjuvant setting, upon completion of chemotherapy or chemoradiation, patients should be monitored for any long-term therapy-related complications.

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**Systemic Therapy for Metastatic or Locally Advanced Cancer**

(Where local therapy is not indicated)

**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.

- Preferred Regimens:
  - Fluoropyrimidine (fluorouracil\(^\dagger\) or capecitabine) and cisplatin (category 1)
  - Fluoropyrimidine (fluorouracil\(^\dagger\) or capecitabine) and oxaliplatin

\(^\dagger\)Leucovorin is indicated with certain 5-FU-based regimens. For important information regarding the leucovorin shortage, see Discussion.

- Other Regimens:
  - Paclitaxel with cisplatin or carboplatin
  - Docetaxel with cisplatin
  - Fluoropyrimidine (fluorouracil\(^\dagger\) or capecitabine)
  - Docetaxel
  - Paclitaxel
  - Fluorouracil\(^\dagger\) and irinotecan (category 1)
  - DCF modifications
    - Docetaxel, cisplatin, and fluorouracil
    - Docetaxel, oxaliplatin, and fluorouracil\(^\dagger\)
    - Docetaxel, carboplatin, and fluorouracil (category 2B)
    - ECF (epirubicin, cisplatin, and fluorouracil) (category 1)
    - ECF modifications (category 1)
      - Epirubicin, oxaliplatin, and fluorouracil
      - Epirubicin, cisplatin, and capecitabine
      - Epirubicin, oxaliplatin, and capecitabine

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Only the following drugs have been approved:

**Docetaxel** in first line

**Trastuzumab** in the first line with other cytotoxics

**Ramucirumab** (alone or with paclitaxel) in second line
Metastatic GAC

Drugs that are grandfathered in and still useful:

- Fluoropyrimidines Any line
- Platinum compounds First line
- Irinotecan in second or third line

Metastatic GAC

Agents that are not recommended:

- Epirubicin Any line
- Mitomycin Any line
Metastatic GAC

Standard of care recommendations:

Add trastuzumab to 2-drug cytotoxic combo for Her2 positive GAC patients in the front line

Otherwise

Platinum plus fluoropyrimidine in the first line
Paclitaxel/ramucirumab in the second line and Irinotecan plus/minus fluoropyrimidine in the third line

Some general principles when treating these patients:

Two drugs are better than one (Spirits trial)
Three drugs are not necessarily better than two
Do not use ramucirumab alone (not effective)
If possible, always consider paclitaxel/ramucirumab
Do not recommend taxane in the first line
Do not recommend epirubicin at all
No benefit for anthracycline

- Peri-operative chemotherapy:

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Pts</th>
<th>Treatment</th>
<th>Surgery-only</th>
<th>Peri-op chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAGIC</td>
<td>503</td>
<td>ECF</td>
<td>5-yr 23%</td>
<td>5-yr 36%</td>
</tr>
<tr>
<td>FNCLCC/FFCD</td>
<td>224</td>
<td>5-FU/Cis</td>
<td>5-yr 24%</td>
<td>5-yr 38%</td>
</tr>
</tbody>
</table>

- Adjuvant chemoradiation:
  - CALGB 80801 study: 5-FU/LV + chemoRT vs. ECF + chemoRT

1. Cunningham, NEJM 2008;359:11
2. Yehou, J Clin Oncol 2011;29:1715
3. Fuchs, J Clin Oncol 2011;29:4003 [abstr]

OEO5 Trial Design

- Histologically confirmed adenocarcinoma lower oesophagus and GOJ (Type I and II)
- MDT - resectable following EUS and CT
- (excluded T1/2 N0)

- CF: Two 3-weekly cycles of cisplatin (80mg/m² D1) and 5FU (1g/m² D 1-4)
- ECX: Four 3-weekly cycles of epirubicin (50mg/m² D1), cisplatin (60mg/m² D1) and capecitabine (1250mg/m² daily)

### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CF (N=451)</th>
<th>ECX (N=446)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Median (Range)</td>
<td>62 (27 – 81)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Male</td>
<td>412 91%</td>
</tr>
<tr>
<td><strong>WHO PS</strong></td>
<td>0</td>
<td>311 69%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>140 31%</td>
</tr>
<tr>
<td><strong>Stage (TNM6)</strong></td>
<td>T1 N1</td>
<td>3 1%</td>
</tr>
<tr>
<td></td>
<td>T2 N1</td>
<td>49 11%</td>
</tr>
<tr>
<td></td>
<td>T3 N0</td>
<td>97 22%</td>
</tr>
<tr>
<td></td>
<td>T3 N1</td>
<td>287 64%</td>
</tr>
<tr>
<td></td>
<td>T4 N0</td>
<td>3 1%</td>
</tr>
<tr>
<td></td>
<td>T4 N1</td>
<td>12 3%</td>
</tr>
<tr>
<td><strong>Laparoscopy</strong></td>
<td>Yes</td>
<td>216 48%</td>
</tr>
<tr>
<td><strong>PET</strong></td>
<td>Yes</td>
<td>271 60%</td>
</tr>
</tbody>
</table>


### Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Median survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CF</strong></td>
<td>2.02 (1.80, 2.38)</td>
</tr>
<tr>
<td><strong>ECX</strong></td>
<td>2.15 (1.93, 2.53)</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>0.92 (0.79, 1.08)</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.8582</td>
</tr>
</tbody>
</table>

3-year survival (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>CF (39% (35%, 44%))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECX</strong></td>
<td>42% (37%, 46%)</td>
</tr>
</tbody>
</table>

Key Features of Gastric Cancer Subtypes

- **CIN**
  - Intestinal tumours
  - PTEN mutation
  - RAS activation

- **EBV**
  - PIK3CA mutation
  - PD-L1/2 overexpression
  - EBV-CIMP
  - CDX2 silencing
  - Immune cell signalling

- **MSI**
  - Hypermutation
  - Gastric-CIMP
  - MLH1 silencing
  - Mitotic pathways

- **GS**
  - Diffuse tumours
  - CDH1, RHOA mutations
  - CDKN1A-ARF/TP53 fusion
  - Cell adhesion

- **n=295**

Differences in Clinical and Histological Characteristics Among Subtypes

- **Lauren classification**
  - Diffuse (%)

- **Number of samples**

- **Males (%)**

- **Age at initial diagnosis**
Molecular Characteristics of EBV-positive Gastric Cancers

The proportion of tumors harboring PIK3CA mutation in the molecular subtypes with mutations at sites noted recurrently in this data set or in the COSMIC database marked separately.

Red = Amplifications and Green = Mutations

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Molecular Analysis of Gastric Cancer


Molecular Analysis of Gastric Cancer


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Molecular Subtype and Survival Association


Immune System and Gastroesophageal Adenocarcinoma

Bhardwaj, N. J Clin Invest. 2007;117(5):1130-1136
Three dimensional structures of MHC-I and MHC-II molecules with peptide ligands.


Cells that have MHC-Class II molecules

Professional APCs

DCs and macrophages

Key features
- Phagocytic
- Express receptors for apoptotic cells, DAMPs and PAMPs
- Localize to tissues
- Localize to T cell zone of lymph nodes following activation (DCs)
- Constitutively express high levels of MHC class II molecules and antigen processing machinery
- Express co-stimulatory molecules following activation

Atypical APCs

Mast cells, Basophils, Eosinophils, ILC3s

Key features
- Inducible expression of MHC class II molecules
- Antigen-presenting functions limited to specific immune environments (especially type 2 immune settings)
- Lack of compelling evidence that they can activate naïve CD4+ T cells in an antigen-specific manner

B cells

Key features
- Internalize antigens via BCRs
- Constitutively express MHC class II molecules and antigen processing machinery
- Express co-stimulatory molecules following activation

Nature Rev Imm November 2014
MHC-I biosynthesis and antigenic peptide binding in the ER.


Trafficcking of antigens for processing and presentation with MHC molecules: basic pathways and exceptions to the “rules”.

A Phase 1b Study of Pembrolizumab (Pembro; MK-3475) in Patients With Advanced Gastric Cancer

Kei Muro,1 Yung-Jue Bang,2 Veena Shankaran,2 Ravit Geva,4 Daniel Catenacci,5 Shilpa Gupta,6 Joseph Paul Eder,7 Raanan Berger,8 Edward J. Gonzalez,9 Jennifer Pulin,9 Archana Ray,9 Marisa Dolled-Filhart,9 Kenneth Emancipator,9 Kumudu Pathiraja,6 Xinxin Shu,9 Minoru Koshiji,6 Jonathan Cheng,9 Ilyun Cheol Chung10

1Aichi Cancer Center Hospital, Nagoya, Japan; 2Seoul National University Hospital, Seoul, South Korea; 3University of Washington, Seattle, WA, USA; 4Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel; 5University of Chicago, Chicago, IL, USA; 6H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; 7Yale University, New Haven, CT, USA; 8Sheba Medical Center, Tel Hashomer, Israel; 9Merck & Co, Inc, Whitehouse Station, NJ, USA; 10Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea

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KEYNOTE-012: Gastric Cohort

- Recurrent or metastatic adenocarcinoma of the stomach or GEJ
- ECOG PS 0-1
- PD-L1+ tumor
- No systemic steroid therapy
- No autoimmune disease (active or history of)
- No active brain metastases

**Screening:** 65 of 162 (40%) patients assessed for PD-L1 expression had PD-L1+ tumors

**Patients:** 19 patients from Asia and 20 patients from the rest of the world

**Treatment:** 10 mg/kg IV Q2W

**Response assessment:** Performed every 8 weeks per RECIST v1.1

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Maximum Percent Change From Baseline in Tumor Size\(^a\) (RECIST v1.1, Investigator Review)

- 41% of patients experienced a decrease in tumor burden

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Current Trials for Esophagogastric Cancer

<table>
<thead>
<tr>
<th>Anti-CTLA-4 or Anti-PD-1 of PD-L1</th>
<th>Perioperative</th>
<th>1L</th>
<th>2L</th>
<th>3L + Refractory to Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab (BMS) Anti-CTLA-4</td>
<td></td>
<td></td>
<td></td>
<td>COMBO w/ Nivo?</td>
</tr>
<tr>
<td>Nivolumab (ONO/BMS) Anti-PD-1</td>
<td>Adjuvant</td>
<td>PH III CTX +/- Nivo</td>
<td>PH III Nivo vs PTX or DTX</td>
<td>NCT04538-07 Ph II Nivo</td>
</tr>
<tr>
<td>Pembrolizumab (MSD) Anti-PD-1</td>
<td>Keynote-061</td>
<td>PH III Pembrol vs FC 5-FU</td>
<td>Keynote-061 Ph III Pembrol vs PTX</td>
<td>Keynote-061 Ph II Keynote-069 Ph III</td>
</tr>
<tr>
<td>Durvalumab (AZ) Anti-PD-L1</td>
<td>Adjuvant</td>
<td>PH II NCT0250453 Ph II Durva vs placebo</td>
<td>NCT0234075 Ph Ib / II Durva + Tremel vs combo</td>
<td>Durva + Tremel</td>
</tr>
<tr>
<td>Atezolizumab (Roche) Anti-PD-L1</td>
<td>Perioperative PH II Durva / placebo</td>
<td>NCT0234075 Ph Ib / II Durva + Tremel</td>
<td>NCT0234075 Ph Ib / II Durva + Tremel</td>
<td></td>
</tr>
<tr>
<td>Avelumab (Merck Serono/Pfizer) Anti-PD-L1</td>
<td>Javelin GASTRIC 100 PH III Maintenance after FOLFOX</td>
<td>NCT01772004 (Ph I) / III Ave</td>
<td>Javelin GASTRIC 300</td>
<td></td>
</tr>
</tbody>
</table>


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ASCOGI2015

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>RAM N/Revs N/Revs</th>
<th>PBO4C Median (months)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>REGARD Overall survival PBO4C</td>
<td>6.2</td>
<td>Cmin,1 Low vs PBO4C 36 / 24 35 / 27 5.6</td>
<td>0.891 (0.496, 1.602)</td>
<td>0.7008</td>
</tr>
<tr>
<td>Cmin,1 High vs PBO4C 36 / 17 35 / 27 11.0</td>
<td>0.362 (0.185, 0.711)</td>
<td>0.0032</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Cmin,1 = minimum concentration following the first dose; CI = confidence interval; N = total number of patients; OS = overall survival; PBO4C = patients in placebo arm who had at least 4 cycles of treatment; LowHigh = RAM-treated patients with Cmin,1 < or ≥31.705 µg/mL (median), respectively.

Taberno J et al. J Clin Oncol. 2015;33(Suppl 3); Abstract 121
### REGARD Progression-free Survival

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>RAM N/#events</th>
<th>PBO4C N/#events</th>
<th>Median (months)</th>
<th>Hazard Ratioa (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO4C</td>
<td></td>
<td></td>
<td>2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C_{\text{min},1}) Low vs PBO4C</td>
<td>36 / 25</td>
<td>35 / 30</td>
<td>2.8</td>
<td>0.701 (0.399, 1.232)</td>
<td>0.2168</td>
</tr>
<tr>
<td>(C_{\text{min},1}) High vs PBO4C</td>
<td>36 / 27</td>
<td>35 / 30</td>
<td>5.2</td>
<td>0.369 (0.197, 0.692)</td>
<td>0.0019</td>
</tr>
</tbody>
</table>

Abbreviations: \(C_{\text{min},1}\) = minimum concentration following the first dose; CI = confidence interval; N = total number of patients; PFS = progression-free survival; PBO4C = patients in placebo arm who had at least 4 cycles of treatment; Low/High = RAM-treated patients with \(C_{\text{min},1}\) < or \(\geq\) 31.705 µg/mL (median), respectively. Adjusted for peritoneal metastasis, ECOG PS, and location of primary tumor.

---

### RAINBOW Overall Survival

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>RAM+PAC N/#events</th>
<th>PBO+PAC N/#events</th>
<th>Median (months)</th>
<th>Hazard Ratioa (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO+PAC</td>
<td></td>
<td></td>
<td>7.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAM+PAC Q1</td>
<td>80/68</td>
<td>335/260</td>
<td>6.5</td>
<td>1.039 (0.786, 1.372)</td>
<td>0.7891</td>
</tr>
<tr>
<td>RAM+PAC Q2</td>
<td>80/67</td>
<td>335/260</td>
<td>8.6</td>
<td>0.840 (0.637, 1.108)</td>
<td>0.2168</td>
</tr>
<tr>
<td>RAM+PAC Q3</td>
<td>80/58</td>
<td>335/260</td>
<td>11.6</td>
<td>0.686 (0.514, 0.916)</td>
<td>0.0107</td>
</tr>
<tr>
<td>RAM+PAC Q4</td>
<td>81/57</td>
<td>335/260</td>
<td>12.3</td>
<td>0.533 (0.398, 0.714)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviations: RAM = ramucirumab; PAC = paclitaxel and cisplatin; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile. Adjusted for Eastern Cooperative Oncology Group performance status, weight loss, number of metastatic sites, presence of ascites, tumor differentiation, prior gastrectomy, and region.

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**RAINBOW Multivariate Cox Regression and Kaplan-Meier Analysis of PFS by \(C_{\text{min},1}\) Quartile**

**ASCOGI2015**

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>RAM+PAC</th>
<th>PBO+PAC</th>
<th>Median (months)</th>
<th>Hazard Ratio(^a) (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAM+PAC Q1</td>
<td>80/69</td>
<td>335/296</td>
<td>2.9</td>
<td>0.839 (0.643, 1.096)</td>
<td>0.1985</td>
</tr>
<tr>
<td>RAM+PAC Q2</td>
<td>80/73</td>
<td>335/296</td>
<td>4.6</td>
<td>0.661 (0.508, 0.860)</td>
<td>0.0021</td>
</tr>
<tr>
<td>RAM+PAC Q3</td>
<td>80/67</td>
<td>335/296</td>
<td>4.5</td>
<td>0.626 (0.479, 0.820)</td>
<td>0.0007</td>
</tr>
<tr>
<td>RAM+PAC Q4</td>
<td>81/65</td>
<td>335/296</td>
<td>6.8</td>
<td>0.405 (0.307, 0.535)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(^a\)Adjusted for sex, weight loss, number of metastatic sites, and liver metastasis.

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**Disappointments**

- **mTOR inhibitors**
- **EGFR inhibitors**
- **c-MET inhibitors**
- **Lapatinib and T-DM1** (Her2 positive pts)

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**Metastatic GAC**

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**RAINBOW Progression-free Survival**

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Progression-Free Survival Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>0.95</td>
</tr>
<tr>
<td>4</td>
<td>0.90</td>
</tr>
<tr>
<td>6</td>
<td>0.85</td>
</tr>
<tr>
<td>8</td>
<td>0.80</td>
</tr>
<tr>
<td>10</td>
<td>0.75</td>
</tr>
<tr>
<td>12</td>
<td>0.70</td>
</tr>
<tr>
<td>14</td>
<td>0.65</td>
</tr>
<tr>
<td>16</td>
<td>0.60</td>
</tr>
<tr>
<td>18</td>
<td>0.55</td>
</tr>
<tr>
<td>20</td>
<td>0.50</td>
</tr>
<tr>
<td>22</td>
<td>0.45</td>
</tr>
<tr>
<td>24</td>
<td>0.40</td>
</tr>
</tbody>
</table>
Metastatic GAC

Promising leads

**FGFR2 inhibitors**

**BET-bromodomain inhibitors**

**Coached (activated) T-cell therapy**

**Peptide Vaccine therapy**