Integrating New Therapies into Treatment Regimens for Gastric and Gastroesophageal Cancer

Educational Objectives

- Evaluate the current evidence across multiple lines of therapy and appropriately sequence therapies for gastric and gastroesophageal (GEJ) cancers
- Mitigate toxicities associated with gastric cancer treatment regimens to improve patient outcomes
- Evaluate the safety and efficacy data for emerging therapies for gastric and GEJ cancers.

Agenda

- Introduction
- Overview
  - Treatment in first-line setting
  - Treatment in second-line setting
  - Treatment in third-line setting
  - Role of approved biologics
  - Emerging therapies
  - Side effect management
- Questions and Answers

Worldwide Incidence

Gastric Cancer Statistics

Gastric Adenocarcinoma: Risk Factors

- Nutritional
  - Low fat or protein consumption
  - High consumption of salted, smoked, or preserved foods
  - High nitrate consumption
  - Low consumption of fruits, vegetables
- Medical
  - Previous gastric surgery
  - Helicobacter pylori infection (2x)
  - Chronic atrophic gastritis
- Environmental
  - P. Helicobacter pylori infection (2x)
  - Poor food preparation (smoked)
  - Lack of refrigeration
  - Poor drinking water (eg, well water)
  - Occupation (eg, rubber, coal workers)
  - Cigarette smoking (1.6x)
- Hereditary Factors
  - Germline CDH1 mutation
  - Impaired function in Mismatch repair genes (MLH1)
  - Inactivating mutations in BRCA gene

National Cancer Institute: Gastric Cancer Treatment PDQ.


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Integrating New Therapies into Treatment Regimens for Gastric and Gastroesophageal Cancer

**STAGING: AJCC TNM Classification for Gastric Cancer**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor</th>
<th>Node</th>
<th>Metastasis</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>T1-2</td>
<td>N0-1</td>
<td>M0</td>
<td>Primary tumor, no secondary tumor, no metastasis</td>
</tr>
<tr>
<td>B</td>
<td>T3-4</td>
<td>N0-1</td>
<td>M0</td>
<td>Primary tumor, secondary tumor, no metastasis</td>
</tr>
<tr>
<td>C</td>
<td>T1-2</td>
<td>N2-3</td>
<td>M0</td>
<td>Primary tumor, secondary tumor, metastasis</td>
</tr>
<tr>
<td>D</td>
<td>T1-2</td>
<td>N0</td>
<td>M1</td>
<td>Primary tumor, no secondary tumor, metastasis</td>
</tr>
<tr>
<td>D</td>
<td>T3-4</td>
<td>N0</td>
<td>M1</td>
<td>Primary tumor, secondary tumor, metastasis</td>
</tr>
<tr>
<td>D</td>
<td>T1-2</td>
<td>N1</td>
<td>M1</td>
<td>Primary tumor, secondary tumor, metastasis</td>
</tr>
<tr>
<td>D</td>
<td>T3-4</td>
<td>N2-3</td>
<td>M1</td>
<td>Primary tumor, secondary tumor, metastasis</td>
</tr>
</tbody>
</table>

**Histological Classification**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Diffuse</td>
<td>Tumor cells with pleomorphic nuclei</td>
</tr>
<tr>
<td>Intestinal</td>
<td>Tumor cells with well-differentiated nuclei</td>
</tr>
</tbody>
</table>

**Molecular Subtypes**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Genetically stable</th>
<th>(M_0)</th>
<th>(M_0)</th>
<th>(M_1)</th>
<th>(M_1)</th>
</tr>
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<tbody>
<tr>
<td>TNM</td>
<td>(\text{high} )</td>
<td>(\text{low} )</td>
<td>(\text{low} )</td>
<td>(\text{low} )</td>
<td>(\text{high} )</td>
</tr>
</tbody>
</table>

**The Role of Chemotherapy in Advanced Gastric Cancer**

- Survival with best supportive care (BSC) alone ~ 3 months
- Chemotherapy affords survival in metastatic gastric cancer
- Benefit in weighted mean survival ~ 6 months

**Multidisciplinary Care of Gastric and Locally Advanced GEJ Cancer**
Integrating New Therapies into Treatment Regimens for Gastric and Gastroesophageal Cancer

Role of Surgery in Treatment of Gastric Cancer

Surgical Treatment of Locally Advanced Esophageal Cancer

First-Line Chemotherapy

Phase III Trials Supporting Standard Practice in Advanced Gastric Cancer

REAL 2: Study Design

REAL-2 Results

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**ECF vs EOX**

<table>
<thead>
<tr>
<th>Arm</th>
<th>OS (m)</th>
<th>1 year survival</th>
<th>p-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECF</td>
<td>9.9</td>
<td>37.7 (31.8-31.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EOX</td>
<td>11.2</td>
<td>46.8 (40.4-52.9)</td>
<td>0.020</td>
<td>0.80 (0.66-0.97)</td>
</tr>
</tbody>
</table>

Cunningham et al. NEJM 2008

**Phase III Trial in Metastatic Gastroesophageal Adenocarcinoma with Fluorouracil, Leucovorin Plus Either Oxaliplatin or Cisplatin**

**V-325 Study Design**

Kaplan-Meier estimates of (A) time to progression and (B) overall survival among chemotherapy-naïve advanced gastric cancer patients treated with docetaxel, cisplatin, and fluorouracil (DCF) or cisplatin and fluorouracil (CF; full analysis population).

Eric Van Cutsem; Vladimir M. Moiseyenko; Sergei Tjulandin; Alejandro Majlis; Manuel Constenla; Corrado Boni; Adriano Rodrigues; Miguel Fodor; Yee Chao; Edouard Voznyi; Marie-Laure Risse; Jaffer A. Ajani; JCO 2006, 24, 4991-4997. DOI: 10.1200/JCO.2006.06.8429 Copyright © 2006 TAX 325 Study Results

**ECF vs FOLFIRI**

Time-to-treatment failure (TTF) according to treatment arm (Kaplan-Meier estimation). EOX arm: epirubicin, cisplatin, and capecitabine as the first-line treatment; FOLFIRI arm: irinotecan, leucovorin, fluorouracil bolus, and continuous infusion as the first-line treatment. HR, hazard ratio.

Rosine Guimbaud; Christophe Louvet; Pauline Ries; Marc Ychou; Emilie Maillard; Thierry André; Jean-Marc Gornet; Thomas Aparicio; Suzanne Nguyen; Ahmed Azzedine; Pierre-Luc Etienne; Eveline Boucher; Christine Rebischung; Pascal Hammel; Philippe Rougier; Laurent Bedenne; Olivier Bouché; JCO 2014, 32, 3520-3526. DOI: 10.1200/JCO.2013.54.1011

**Treatment of Metastatic Disease (1st Line)**

<table>
<thead>
<tr>
<th>OX / ECO / EDP</th>
<th>Cape / ECO / EOX</th>
<th>XP</th>
<th>FLO</th>
<th>FOLFR</th>
<th>5-FU / Ca</th>
<th>DCF</th>
<th>ECP</th>
</tr>
</thead>
<tbody>
<tr>
<td>#Pts</td>
<td>498</td>
<td>513</td>
<td>160</td>
<td>103</td>
<td>170</td>
<td>335</td>
<td>221</td>
</tr>
<tr>
<td>1RRR</td>
<td>44%</td>
<td>49%</td>
<td>41%</td>
<td>34%</td>
<td>32%</td>
<td>54%</td>
<td>36%</td>
</tr>
<tr>
<td>TTF, months</td>
<td>0.7</td>
<td>6.5</td>
<td>5.6</td>
<td>5.5</td>
<td>5.0</td>
<td>6.0</td>
<td>5.6</td>
</tr>
<tr>
<td>OS, months</td>
<td>10.9</td>
<td>10.4</td>
<td>10.5</td>
<td>10.7</td>
<td>9.0</td>
<td>13.0</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Integrating New Therapies into Treatment Regimens for Gastric and Gastroesophageal Cancer

Trastuzumab + Chemotherapy in Advanced HER2+ Gastric Cancer: ToGA

Primary endpoint: OS

- Patients with advanced gastric cancer screened for HER2 status (n = 810; 22% of successful screenings)
- Trastuzumab + Chemotherapy in Advanced HER2+ Gastric Cancer: ToGA
  - Primary endpoint: OS
  - Selected at investigator’s discretion: 5-FU 800 mg/m2/day infusional on Days 1-5 q3w x 6; capecitabine 1000 mg/m2 BID on Days 1-14 q3w x 6.

Key Points First Line Treatment

- Chemotherapy with platinum compound (cisplatin, oxaliplatin) plus a fluoropyrimidine (fluorouracil [5-FU], capecitabine, or S-1) is the global standard
- Selective patients can benefit from triplet combinations but increased side effects must be considered. Overtoxic treatments like docetaxel-containing triplet regimens cannot be recommended in older patients.
- Oxaliplatin and irinotecan can substitute for cisplatin without compromising the efficacy of chemotherapy
- Trastuzumab in combination with chemotherapy is the recommended treatment for patients with HER2+ tumors 3+ by IHC or 2+IHC + FISH positive.

Second Line Chemotherapy

- Phase III REGARD Trial
  - BSC ± Ramucirumab in Metastatic Gastric or GEJ Cancer
    - Primary objective: OS
    - Secondary endpoints: PFS, 12-wk PFS, ORR, DOR, QoL, safety

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**REGARD Trial of BSC ± Ramucirumab in Metastatic Gastric or GEJ Cancer: OS**

- **Pts at Risk, n**
  - Ramucirumab: 238
  - Placebo: 117

- **Proportion Remaining Alive**
  - **Mos**
    - Ramucirumab: 5.2 (4.4-5.7)
    - Placebo: 3.8 (2.8-4.7)
  - **6-mo OS, %**
    - Ramucirumab: 42
    - Placebo: 32
  - **12-mo OS, %**
    - Ramucirumab: 18
    - Placebo: 11
  - **HR: 0.776 (95% CI: 0.603-0.998; P = .0473)**

**REGARD Trial of BSC ± Ramucirumab in Metastatic Gastric or GEJ Cancer: PFS**

- **Pts at Risk, n**
  - Ramucirumab: 238
  - Placebo: 117

- **Proportion Without Progression**
  - **Mos**
    - Ramucirumab: 2.1 (1.5-2.7)
    - Placebo: 1.3 (1.3-1.4)
  - **12-wk PFS, %**
    - Ramucirumab: 40
    - Placebo: 16
  - **HR: 0.483 (95% CI: 0.376-0.620; P < .0001)**

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**RAINFOW Study**

- **Ramucirumab 8 mg/kg day 1&15**
- **Paclitaxel 80 mg/m² day 1, 8 & 15 of a 28-day cycle**
- **N = 330**
- **Placebo day 1&15**
- **Paclitaxel 80 mg/m² day 1, 8 & 15**
- **N = 335**

**Important inclusion criteria:**
- Metastatic or loc. adv. unresectable gastric or GEJ* adenocarcinoma
- Progression after 1st line platinum/fluoropyrimidine-based chemotherapy

**Stratification factors:**
- Geographic region
- Measurable vs non-measurable disease
- Time to progression on 1st line therapy (< 6 mos vs. ≥ 6 mos)

*GEJ= gastroesophageal junction; gastric and GEJ will be summarized under the term GC


- **ΔmOS difference: 2.3 months**
- **RAM + PTX PBO + PTX**
  - **Patients / Events**
    - RAM + PTX: 330 / 256
    - PBO + PTX: 335 / 260
  - **Median (mos) (95% CI)**
    - RAM + PTX: 9.63 (8.48, 10.81)
    - PBO + PTX: 7.36 (6.31, 8.38)
  - **6-month OS**
    - RAM + PTX: 72%
    - PBO + PTX: 57%
  - **12-month OS**
    - RAM + PTX: 40%
    - PBO + PTX: 30%

- **RAM = ramucirumab; PTX = paclitaxel; PBO = placebo.**

---

**The Role of Biologics**

### HER-2 Inhibition

<table>
<thead>
<tr>
<th>Trial</th>
<th>Line of Therapy</th>
<th>Drug</th>
<th>Patient Selection</th>
<th>Survival</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ToGA</td>
<td>1st Line</td>
<td>Trastuzumab + Cis + 5FU vs Cis + 5FU</td>
<td>HER2+</td>
<td>15.6 mos vs 11.1 mos</td>
<td>FDA approved in 2010</td>
</tr>
<tr>
<td>LOGIC</td>
<td>1st Line</td>
<td>Cis + Lapatinib vs Cis + Placebo</td>
<td>HER2+</td>
<td>12.2 mos vs 10.3 mos</td>
<td>No improvement in PFS or OS</td>
</tr>
<tr>
<td>ZAINZER</td>
<td>1st Line</td>
<td>Pertuzumab + Trastuzumab + chemo vs Trastuzumab + chemo</td>
<td>HER2+</td>
<td>17.5 mos vs 14.2 mos</td>
<td>NS</td>
</tr>
<tr>
<td>TYPHON</td>
<td>2nd/3rd Line</td>
<td>Lapatinib + Paclitaxel vs Paclitaxel alone</td>
<td>HER2+</td>
<td>11.3 mos vs 8.4 mos</td>
<td>Did not improve OS significantly</td>
</tr>
<tr>
<td>GATSBY</td>
<td>2nd/3rd Line</td>
<td>Trastuzumab + Lapatinib vs Trastuzumab alone</td>
<td>HER2+</td>
<td>7 months for T-DM1 vs 6.6 mos for capecitabine &amp; capecitabine + docetaxel</td>
<td>No efficacy</td>
</tr>
</tbody>
</table>

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**Activity Slides**

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EGFR Inhibition / EGFR Targeting
- Targeted Agents Phase III: Negative Trials for EGFr
- REAL 3: ECX + / - Panitumumab (U.K.): Negative: Panitumumab had inferior outcomes
- EXPAND: Cape-Cis + / - Cetuximab (E.U.) – Negative: Cetuximab trended inferior
- COG: BSC vs Gefitinib (U.K.): Negative
- Trials conducted with no biomarker
- Selection of patients
- No biomarker identified in EG Cancer

EGFR

Hepatocyte Growth Factor

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Drugs</th>
<th>Patient Selection</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rilotu-1</td>
<td>Rilotumumab + ECX vs ECX</td>
<td>MET+/HER2-</td>
<td>Closed due to toxicity</td>
</tr>
<tr>
<td>Rilotu-2</td>
<td>Rilotumumab + CA vs CA</td>
<td>MET+/HER2-</td>
<td>Closed due to toxicity</td>
</tr>
<tr>
<td>MET Gastric</td>
<td>Oratulimumab + FOLFIRI vs FOLFOX</td>
<td>MET+/HER2-</td>
<td>Effective</td>
</tr>
</tbody>
</table>

| Phase II      | Sorafenib                      | Unselected        | No improvement in PFS or OS |

Figure from Oncotarget, 2017, Vol 8 (No 34), pp: 57654-57669

VEGF/VEGFR Pathway

<table>
<thead>
<tr>
<th>Trial</th>
<th>Line of Therapy</th>
<th>Drugs</th>
<th>Patient Selection</th>
<th>Survival</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVA-1</td>
<td>1st Line</td>
<td>XP + Bevacizumab</td>
<td>No selection</td>
<td>12.1 mos vs 10.1 mos</td>
<td>1.2 mos to 1.0; P &gt; 0.002</td>
</tr>
<tr>
<td>REGARD</td>
<td>2nd Line</td>
<td>Ramucirumab + BSC</td>
<td>No selection</td>
<td>5.3 mos vs 3.8 mos</td>
<td>p&lt;0.047</td>
</tr>
<tr>
<td>RAINBOW</td>
<td>2nd Line</td>
<td>Pazopanib + Ram</td>
<td>No selection</td>
<td>9.6 mos vs 7.4 mos</td>
<td>hazard ratio 0.87; 95% CI 0.73 to 1.03; P = 0.052</td>
</tr>
<tr>
<td>Phase III</td>
<td>3rd Line</td>
<td>Apatinib vs Placebo</td>
<td>No selection</td>
<td>195 days vs 140 days</td>
<td>Improvement in PFS/OS Asian study</td>
</tr>
</tbody>
</table>

Emerging Therapies

Immunotherapy Approaches in GEJ Cancer

Immuno -therapy

Specific
- Cancer Vaccines
- FGFR
- EGFR
- Passive
- Checkpoint Inhibition
- PD1
- CTLA-4
- Non-specific
- Monoclonal antibodies
- Trastuzumab
- Ramucirumab
- ACT
- CTL
- TIL
- CART-T

Cancer Vaccines

Aim to prime and expand tumor-specific T cells by delivering tumor antigens to drive effective T cell activation.
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Cancer Vaccines

- Early phase studies of a DC vaccine combined with HER2 peptide in a small group of advance HER-2 positive patients and a pulsed DC MAGE3 peptide vaccine appeared to show modes effect.
- Further clinical development of DC-based vaccine approaches has been limited.

Adoptive Cell Therapy

In ACT, tumor-specific T cells are isolated from a patient, amplified and primed in vitro to tumor antigens or through genetic modification before being transfused into the patient.

Immune Checkpoint Inhibitors

Immune Checkpoints

CTLA-4 and PD-1/PD-L1

CTL-4 Directed Approaches

<table>
<thead>
<tr>
<th>Phase</th>
<th>Drug</th>
<th>No of pts</th>
<th>Line of Therapy</th>
<th>Outcome</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Tremelimumab (CTLA-4 antibody)</td>
<td>18</td>
<td>2nd/3rd line</td>
<td>ORR: 5%</td>
<td>TTP: 2.83 months</td>
</tr>
<tr>
<td>NCT01585987</td>
<td>Ipilimumab (CTLA-4 ab) vs best supportive care</td>
<td>114</td>
<td>Sequential after 1st line</td>
<td>PFS: 2.92 vs 4.89 (mos)</td>
<td>OS: 16.75 vs. 12.05 (mos)</td>
</tr>
<tr>
<td>P=0.0036</td>
<td>P=0.8433</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

PD-1 Directed Approaches

<table>
<thead>
<tr>
<th>Phase</th>
<th>Drug</th>
<th>No of patients</th>
<th>Line of Therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Pembrolizumab (PD-1 antibody)</td>
<td>39</td>
<td>PD-L1+</td>
<td>ORR 22%</td>
</tr>
<tr>
<td>I</td>
<td>Nivolumab (PD-L1 antibody)</td>
<td>16</td>
<td>Any line</td>
<td>ORR 25%</td>
</tr>
<tr>
<td>I/II</td>
<td>Checkmate 032</td>
<td>Nivolumab (PD-1 antibody)</td>
<td>59</td>
<td>&gt;2 lines</td>
</tr>
<tr>
<td>I (Japan)</td>
<td>Avelumab</td>
<td>20</td>
<td>2nd/3rd line</td>
<td>ORR 15%</td>
</tr>
</tbody>
</table>
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**Phase 3 Study of Nivolumab (Nivo) in Previously Treated Advanced Gastric or Gastroesophageal Junction (G/GEJ) Cancer**

Updated results and subset analysis by PD-L1 expression (ATTRACTION-02)

**Response by PDL-1 Expression**

**KEYNOTE-059 (Cohort 1): Survival**

**Response by PD-L1 Expression**

**KEYNOTE-059: Study Design**

Open-label, Multicohort Phase II Study

- Primary endpoints: ORR, safety; secondary endpoints: DoR, PFS, OS
- Exploratory biomarker endpoints: efficacy by MSI, GEP

*HER2/neu positive allowed in cohort 1 if prior trastuzumab administered.

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Checkmate 032 Gastric Cohort

Best Reductions in Target Lesions

Key Points

• Immunotherapy including immune checkpoint inhibition is a growing area of research in gastric and esophageal cancers. Certain tumor characteristics may predict favorable responses to these approaches.

• Checkpoint inhibitor with anti-PD-1 mAb pembrolizumab and nivolumab has led to increased response rates in advanced heavily pre-treated patients

• Higher response rates in PDL-1 expression

• Combination approaches with chemotherapy, radiotherapy and targeted agents are likely to improve outcomes

• Clinical trials applying modern sequence technology that allows for identification of unique, tumor-specific neoantigen profiles are ongoing.

Side Effect and Management

5-Fluorouracil/Capecitabine Toxicity

• Toxicity similar to continuous infusion 5-Fluorouracil

• Common
  - Palmar-plantar erythrodysesthesia (Hand-foot syndrome)
  - Mucositis
  - Diarrhea
  - Photosensitivity

• Rare
  - Nausea/vomiting
  - Hyperbilirubinemia
  - Cardiac toxicity
  - Ocular toxicity

• Grade 2 stop drug until resolved or grade 1. Consider dose reduction.

Oxaliplatin Toxicity

• Two types of neuropathy
  - Acute neuropathy
    - Cold sensitivity for first 5 to 7 days after each dose
  - Chronic neuropathy
    - Dose limiting cumulative peripheral neuropathy

• Moderate emetogenic potential
• Myelosuppression
• Extravasation risk
• Delayed hypersensitivity
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**Prevention and Management of Platinum Induced Nausea and Vomiting**

Level 2: Patients receiving a moderately emetogenic agent or patients receiving mildly emetogenic agent who have failed to respond to or are intolerant of at least two level 1 regimens:

- Aprepitant 125 mg PO before chemotherapy on day 1, then 80 mg PO daily on days 2 and 3, and
- Palonosetron 0.25 mg IV before chemotherapy, and
- Dexamethasone 10-12 mg IV/PO before chemotherapy, then 8 mg PO daily on days 2-4

With or without

- Lorazepam 1 mg PO or IV before q4-6 hrs p.r.n., or
- Prochlorperazine 10 mg PO q4h-6 h p.r.n; or both

**Irinotecan Toxicity**

- Diarrhea
  - Early diarrhea
    - < 24 hours after irinotecan
    - Cholinergic type reaction
      - Anticholinergics (Atropine) can be beneficial
        - Atropine 0.25 -1 mg IV before irinotecan
  - Late diarrhea
    - > 24 hours after irinotecan
    - Prolonged diarrhea if not controlled
    - Aggressive loperamide can be beneficial

- Myelosuppression
- Moderate emetogenic potential
- Mucositis

**Ramucirumab Adverse Effects**

- GI perforation—permanently discontinue
- Thromboembolism
  - ATE—permanently discontinue
  - VTE
    - Continue with full dose anticoagulation with DVT or asymptomatic PE
    - Permanently discontinue if symptomatic PE
- CHF—permanently discontinue
- Delayed wound healing
  - Hold 4-8 weeks prior to and 4-8 weeks after surgery

**Trastuzumab: Adverse Effects**

- Infusion related reactions
  - Occur during or within 24 hours 21-40%
  - Can cause severe pulmonary toxicity (can be delayed)
  - Discontinue if life-threatening severe reactions
  - Cardiotoxicity: LVEF decreased (4-22%)
  - LVEF decreased and congestive heart failure
  - Use caution in patients with heart failure, cardiomyopathy, ventricular dysfunction
  - Recommended to undergo monitoring before and during therapy (MUGA or ECHO)
  - May require holding trastuzumab and CHF treatment

**Side Effects vs Immune Related Adverse Events**

- Immune related adverse event (irAE)
  - Type of side effect
  - Result of immune infiltration and inflammation
  - May be diagnosed with a biopsy of the affected anatomic location
  - May be a diagnosis of exclusion
  - Responsive to corticosteroids

Most common side effects of immunotherapy occur in 20-30% of patients

Immune related adverse events are generally uncommon

**Side Effects: Immunotherapy**

- Dermatological toxicities
  - Rash
  - Follicular dermatitis
  - Vitiligo
  - Bullous pemphigoid
- Endocrine Toxicities
  - Hypophysitis
  - Hypothyroidism
  - Hyperthyroidism
  - Thyroiditis
  - Adrenal Insufficiency
- Hepatic Toxicity
  - Hepatitis
  - Hepatomegaly
- Pneumonitis
  - Acute interstitial pneumonia
  - Diarrhea colitis

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Activity Slides
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Management of Immune-related Adverse Events Excluding Skin and Endocrine Toxicities

Conclusions

- Targeted therapies
  - Biomarkers needed to identify patients
  - Gene amplification > mutation in gastric cancer
  - Trastuzumab: HER2+ amplified gastroesophageal/gastric cancers, only a minority are eligible for HER2 targeting antibody therapy
  - Newer HER2 agents – Pertuzumab trial in the front line did not meet endpoint
  - Ramucirumab + paclitaxel: translated into survival benefit

- Negative trials in unselected patients:
  - EGFR agents + chemo
    - Panitumumab, Cetuximab + chemo detrimental
  - VEGF-A
  - Bevacizumab + chemo
  - cMET trials in selected population: highlight importance of biomarker use

Conclusions (cont)

- Heterogeneity of GC has led to differentiating those tumors that depend on an immune regulatory mechanism: EBV driven tumors and the MSI subtypes.
- Distinct biology subtypes will allow for application of more targeted therapies.
- Developing effective immunotherapy will require further knowledge of the complex relationship between tumor and environment.
- Immunologic checkpoint blockade with anti CTLA-4 and PD-1/PDL-1 have shown promising results. Further combination with immunotherapies might have synergistic effects.

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