ESOPHAGEAL & GASTRIC CANCER

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DISCLOSURES

• No Relevant Financial Disclosures

• Will Discuss Investigational Techniques/Off Label use
Objectives

• Understand the pathophysiology of esophageal and gastric cancer
• Evaluate common presentations of esophageal and gastric cancer
• Management of esophageal and gastric cancer
Epidemiology

• 1960s:
  – Squamous cell carcinoma (SCC) >90%

• 2000’s:
  – Adenocarcinoma >60 (US)

• Worldwide: SCC still predominates
Risk Factors

• SCC:
  – Smoking
  – Alcohol

• Adenocarcinomas:
  – Barrett's esophagus with specialized intestinal metaplasia (GERD)
  – Obesity
  – Smoking
  – GERD
Clinical Vignette

• 75 yo male with h/o smoking and ETOH use presents with progressive dysphagia and odynophagia.

Next step?

EUS
EGD
Cross sectional imaging
Surgery
Clinical Vignette (cont..)

- 75 yo male with h/o smoking and ETOH use presents with progressive dysphagia and odynophagia. EGD demonstrates a 4 cm partially obstructing tumor at the GEJ. Bx: moderately differentiated adenocarcinoma

Next step?
- EUS
- Her2Neu testing
- Cross sectional imaging
- Surgery
Clinical Vignette (cont..)

EUS demonstrates a **T3 lesion** and PET/CT shows uptake in the **2 para esophageal lymphnodes** and no evidence of metastatic disease.

Next step?
- Her2Neu testing
- Neoadjuvant chemoradiation
- Surgery
### Adenocarcinoma carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis (HGD)</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
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<td>M0</td>
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<tr>
<td>IIA</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>T3</td>
<td>N2</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
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<tr>
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<td>T4a</td>
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<td>MO</td>
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<tr>
<td>T4b</td>
<td>Any</td>
<td>M0</td>
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</tr>
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<td>Any</td>
<td>N3</td>
<td>M0</td>
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</tr>
<tr>
<td>IV</td>
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<td>M1</td>
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### Squamous cell carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
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<th>Grade</th>
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<td>1, X</td>
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<tr>
<td>IB</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
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<td>Upper, middle</td>
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<td>M0</td>
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<td>Upper, middle</td>
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<td>M0</td>
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<td>Any</td>
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<td>M0</td>
<td>Any</td>
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<td>M0</td>
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<tr>
<td>T4b</td>
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<tr>
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<td>M0</td>
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<td>Any</td>
<td>Any</td>
<td>M1</td>
<td>Any</td>
<td>Any</td>
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</table>
Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer - CROSS TRIAL


**mOS**: 49.4 vs. 24 (S)mo
**HR**: 0.67, **P=0.003**
B  Survival According to Tumor Type and Treatment Group

![Graph showing survival rates for different tumor types and treatment groups with follow-up in months.]

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
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<tbody>
<tr>
<td>AC, CRT+surgery</td>
<td>134</td>
<td>107</td>
<td>87</td>
<td>53</td>
<td>34</td>
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<tr>
<td>AC, surgery alone</td>
<td>141</td>
<td>99</td>
<td>73</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>SCC, CRT+surgery</td>
<td>41</td>
<td>35</td>
<td>30</td>
<td>21</td>
<td>15</td>
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<tr>
<td>SCC, surgery alone</td>
<td>43</td>
<td>29</td>
<td>19</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>359</td>
<td>270</td>
<td>209</td>
<td>135</td>
<td>82</td>
</tr>
</tbody>
</table>
Management

• **Early stage**: ESD/EMR (T1a)
• **T2N0**: Esophagectomy
• **Node positive/advanced**: Chemo RT – Sx
• **Metastatic**: Palliative chemotherapy
  – Fluropyrimidine plus platinum
  – Her2Neu testing
Epidemiology

• Risk factors
  – H. Pylori
  – Refrigeration
  – Geographic variation
  – Migration patterns
Histology

- **Intestinal** gastric cancer is more common in males and older age groups. It is more prevalent in high-risk areas and is likely linked to environmental factors.

- **Diffuse or infiltrative** type, is equally frequent in both sexes, is more common in younger age groups, and has a worse prognosis than the intestinal type.
Clinical Vignette

• 48 yo male with abdominal discomfort eval by endoscopy noted to have a **distal stomach mass**; poorly differentiated adenocarcinoma. EUS and imaging dem T3N1 disease with **no distant metastasis**.

• What is NOT a SOC option
  – Radiation and chemo followed by Sx
  – Gastrectomy followed by adj ChemoRT
  – Perioperative chemotherapy
  – Gastrectomy followed by chemotherapy
Overall survival with chemotherapy in advanced OG cancer

Presented By Ian Chau at 2017 Gastrointestinal Cancers Symposium

COLORECTAL CANCER
Objectives

• Understand the pathophysiology of CRC
• Evaluate common presentations of suspected CRC
• Management of CRC
# The Problem

## Figure 3. Leading Sites of New Cancer Cases and Deaths – 2016 Estimates

<table>
<thead>
<tr>
<th>Estimated New Cases</th>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td><strong>Female</strong></td>
</tr>
<tr>
<td>Prostate 180,890 (21%)</td>
<td>Breast 246,660 (29%)</td>
</tr>
<tr>
<td>Lung &amp; bronchus 117,920 (14%)</td>
<td>Lung &amp; bronchus 106,470 (13%)</td>
</tr>
<tr>
<td>Colon &amp; rectum 70,820 (8%)</td>
<td>Colon &amp; rectum 63,670 (8%)</td>
</tr>
<tr>
<td>Urinary bladder 58,950 (7%)</td>
<td>Uterine corpus 60,050 (7%)</td>
</tr>
<tr>
<td>Melanoma of the skin 46,870 (6%)</td>
<td>Thyroid 49,350 (6%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma 40,170 (5%)</td>
<td>Non-Hodgkin lymphoma 32,410 (4%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis 39,650 (5%)</td>
<td>Melanoma of the skin 29,510 (3%)</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx 34,780 (4%)</td>
<td>Leukemia 26,050 (3%)</td>
</tr>
<tr>
<td>Leukemia 34,090 (4%)</td>
<td>Pancreas 25,400 (3%)</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct 28,410 (3%)</td>
<td>Kidney &amp; renal pelvis 23,050 (3%)</td>
</tr>
<tr>
<td>All sites 841,390 (100%)</td>
<td>All sites 843,820 (100%)</td>
</tr>
</tbody>
</table>

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

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The ‘Suspected’ Cause - Pathogenesis

- Chromosomal instability
- Microsatellite instability pathway
  - inactivation of DNA mismatch repair proteins
- CpG island methylator pathway (CIMP)
  - underlies MSI associated with MLH1 hypermethylation
Potential Risk Reduction Strategies

• Less Red

• Regular PE

• BMI

• Avoidance of ETOH

• 5-7 servings of fresh fruits and vegetables

NONE OF THESE HAVE SHOWN TO BE AS EFFECTIVE AS SCREENING
## Staging

### TNM staging for colorectal cancer, 7th edition

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ: intraepithelial or invasion of lamina propria*</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades through the muscularis propria into pericolorectal tissues</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor penetrates to the surface of the visceral peritoneum</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor directly invades or is adherent to other organs or structures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph node (N)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in 1-3 regional lymph nodes</td>
</tr>
<tr>
<td>N1a</td>
<td>Metastasis in one regional lymph node</td>
</tr>
<tr>
<td>N1b</td>
<td>Metastasis in 2-3 regional lymph nodes</td>
</tr>
<tr>
<td>N1c</td>
<td>Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized parietal or periluminal tissues without regional nodal metastasis</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in four or more regional lymph nodes</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in 4-6 regional lymph nodes</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in seven or more regional lymph nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant metastasis (M)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Metastasis confined to one organ or site (eg, liver, lung, ovary, nonregional node)</td>
</tr>
<tr>
<td>M1b</td>
<td>Metastases in more than one organ/site or the peritoneum</td>
</tr>
</tbody>
</table>
Clinical Vignette

• 45 yo female undergoes a Rt hemicolecotomy for a largeT3 poorly differentiated tumor. 0/35 LN. Here to discuss adjuvant therapy:

Which statement is accurate

– RAS mutation Analysis can guide adjuvant therapy decision

– Stage II MSI high tumors have an excellent prognosis and don’t req adjuvant Rx

– Most cases of MSI-H tumors occur as a manifestation of Lynch syndrome
Management

• Stage I: surgery alone
• Stage II:
  – low risk vs. high risk
  Surgery +/- Adjuvant chemo
• Stage III: Surgery plus adjuvant chemotherapy
• Stage IV: Palliative Chemotherapy
Stage II

• High Risk:
  – T4 primary
  – Inadequately sampled lymph nodes (less than 13 in the surgical specimen)
  – Bowel obstruction or perforation
  – High-grade/poorly differentiated histology
  – Lymphovascular invasion (LVI)
  – Perineural invasion (PNI)
  – Close, indeterminate, or positive margins
  – High preoperative serum carcinoembryonic antigen (CEA) level
What about MSI and Stage II

• MSI-H:
  – **Hypermutability** that occurs due to a deficiency in the DNA MMR
  – DNA Replication with *accumulated errors*
  – Microsatellites aka repeated sequences of DNA
  – MSI can be
    • **Sporadic**-15%; due to hypermethylation of the MLH1 gene promoter
    • **Genetic**-Lynch syndrome; germline mutation in MLH1, MSH2, MSH6, PMS2
• MSI-H (IHC or PCR) portends to a better prognosis and don't respond to 5-FU based regimens*

• Popat et al# in a systematic review of 32 studies of CRC demonstrated that MSI-H pts derived no benefit from adjuvant FU-containing chemotherapy

• Sargent et al^ demonstrated that MSI-H pts treated with chemotherapy was associated with a reduced OS

*Ribic CM, NEJM,2003; #Popat S, JCO,2005;^Sargent DJ, JCO 2010
Stage IV

- Palliative intent

- 5FU (or capecitabine) and Oxaliplatin
- 5FU (or capecitabine) and Irinotecan
- **YES**-BEVACIZUMAB, CETUXIMAB, PANITUMUMAB, ziv-AFLIBERCEPT, RAMUCIRUMAB
- **NO** Radiation
Adjuvant therapy

• 5FU (or capecitabine) and Oxaliplatin

• **NO** BEVACIZUMAB, CETUXIMAB, PANITUMUMAB, ziv-AFLIBERCEPT, RAMUCIRUMAB

• **NO** Radiation unless its rectal cancer
What about CEA?

• Causes for elevated CEA in an individual without cancer
  – Biliary disease
  – Hepatic injury
  – Pulmonary infections
  – Smokers
  – Bowel disease
Newer biomarkers

• Holy grail of onco-monitoring
• Several modalities of testing incl:
  – Quantitatively or structurally-altered proteins
  – Cancer-associated autoantibodies
  – Cell-free nucleic acids (cfNAs)
  – Circulating tumor cells (CTCs)
  – Cancer derived extracellular vesicles (EVs)
IMMUNOTHERAPY IN ONCOLOGY
History of Cancer Immunotherapy:
Key Milestones

- **1970s**: Discovery of dendritic cell
- **1980s**: Immune component to spontaneous regressions in melanoma
- **1990s**: Adoptive T-cell immunotherapy, IFN-α as adjuvant therapy for melanoma, BCG approved for bladder cancer, Discovery of checkpoint inhibitors
- **2000s**: First tumor-associated antigen cloned (MAGE-1), IL-2 approved for RCC and melanoma (US)
- **2011**: First immunotherapy approved for prostate cancer (sipuleucel-T)
- **2014**: Pembrolizumab and nivolumab approved for advanced melanoma
- **2015**: Nivolumab approved for RCC
- **2016**: Pembrolizumab approved for HNSCC
- **2019**: Nivolumab approved for NSCLC
- **2020**: Atezolizumab approved for advanced UC and metastatic NSCLC

**References in sidenotes:**
www.bannermdanderson.com/
Immune System Function and Immune Response

Identify and destroy foreign or abnormal cells in the body

- Nonspecific
- First line of defense
- WBCs (natural killer cells, neutrophils)
- Activation of adaptive response

### Innate Immunity

- Dendritic cell
- Mast cell
- Macrophage
- Natural killer cell
- Complement protein
- Basophil
- Eosinophil
- Neutrophil
- Granulocytes

### Adaptive Immunity

- B-cell
- T-cell
- Antibodies
- CD4+ T-cell
- CD8+ T-cell

**Immune surveillance:**

- Involves both innate and adaptive immune mechanisms
- Goal of immunotherapy for cancer: to “educate and liberate” underlying anticancer immune responses

Adaptive Immune System: T-Cells

- 4 main types of T-cells
  - Helper T-cells (CD4+)
  - Cytotoxic T-cells (CD8+)
  - Suppressor T-cells (CD4+ Foxp3+ CD25+ Tregs)
  - Memory T-cells (CD4+ or CD8+ CCR7+ CD45RO)

Slide credit: clinicaloptions.com
Tumor Specific Immune Response

1. TUMOR
2. LYMPH NODE
3. Tumor antigen

Dendritic cell

Cytokines

Activated T-cell

Resting T-cell

T-cell clonal expansion
**T-Cell Response: First Signal**

T-Cell Regulation via Multiple Costimulatory and Inhibitory Interactions

- T-cell response to antigen is mediated by peptide-MHCs recognized specifically by TCR (first signal)
- B7 family of membrane-bound ligands binds both activating and inhibitory receptors (second costimulatory signal)
- Targeting CTLA-4 and PD-1 inhibitory receptors has been a major clinical focus

T-Cell Response: Accelerate or Brake?

Activating Signals
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Inhibitory Signals
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

T-Cell Stimulation

T-Cell Inhibition

Targeting Cancer with Immunotherapy

Active immunotherapy
- Peptide vaccine
- DC vaccine
- Genetic vaccine
- IL-2
- IFN
- IL-15
- IL-21

Adoptive cell transfer immunotherapy
- T-cell cloning
- TCR or CAR genetic engineering

Immune agonists
- CD40
- CD137
- OX40

Immune checkpoint inhibitors
- CTLA-4
- PD-1
Response Rates With Anti–PD-1 Antibodies

- ORR
  - Melanoma: 28%
  - NSCLC: 18%
  - Renal cell cancer: 27%

- Confirmed ORR
  - Melanoma: 38% (comparable ± previous ipilimumab)

Immune-Related Adverse Events: Mechanism of Action

• “Achilles heel” of checkpoint inhibitors: autoimmunity via irAEs

• Dysregulation of host immune system leads to unique toxicities of immune checkpoint inhibitors, similar to autoimmune disease
If not vigilant, may result in more serious immune-related AEs
### Ipilimumab (Anti–CTLA-4): Suspected irAEs in Pts With Melanoma

<table>
<thead>
<tr>
<th>irAE, %</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<tbody>
<tr>
<td><strong>Dermatologic</strong></td>
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<td></td>
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<tr>
<td>▪ Pruritus</td>
<td>24.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>▪ Rash</td>
<td>19.1</td>
<td>0.8</td>
<td>0</td>
</tr>
<tr>
<td>▪ Vitiligo</td>
<td>2.3</td>
<td>0</td>
<td>0</td>
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<tr>
<td><strong>Gastrointestinal</strong></td>
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<tr>
<td>▪ Diarrhea</td>
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<tr>
<td>▪ Colitis</td>
<td>7.6</td>
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<td><strong>Endocrine</strong></td>
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<td>▪ Hypothyroidism</td>
<td>1.5</td>
<td>0</td>
<td>0</td>
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<td>▪ Hypopituitarism</td>
<td>2.3</td>
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<td>0.8</td>
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<tr>
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<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>▪ Adrenal insufficiency</td>
<td>1.5</td>
<td>0</td>
<td>0</td>
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<tr>
<td><strong>Hepatic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Increase in ALT</td>
<td>1.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>▪ Hepatitis</td>
<td>0.8</td>
<td>0</td>
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</table>

Nivolumab (Anti–PD-1): Suspected irAEs in Pts with Melanoma

- n = 206 pts with malignant melanoma

<table>
<thead>
<tr>
<th>Suspected irAE, %</th>
<th>All Grades</th>
<th>Grade 3/4</th>
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<tbody>
<tr>
<td>Dermatologic</td>
<td>37.4</td>
<td>1.5</td>
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<tr>
<td>Pruritus</td>
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<td>0.5</td>
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<tr>
<td>Rash</td>
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<td>0.5</td>
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<tr>
<td>Vitiligo</td>
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<td>0</td>
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<tr>
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<td>1.5</td>
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<tr>
<td>Diarrhea</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Colitis</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td>7.3</td>
<td>1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>4.4</td>
<td>0</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>3.4</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suspected irAE, %</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic</td>
<td>3.4</td>
<td>1.5</td>
</tr>
<tr>
<td>ALT increase</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>Bilirubin increase</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1.5</td>
<td>0</td>
</tr>
</tbody>
</table>

Time to Onset of Select First Treatment-Related AE With Nivolumab (Any Grade)

- Majority of treatment-related AEs occurred within first 3 mos of treatment

<table>
<thead>
<tr>
<th>Mos</th>
<th>Skin</th>
<th>Gastrointestinal</th>
<th>Pulmonary</th>
<th>Endocrine</th>
<th>Renal</th>
<th>Hypersensitivity/infusion reaction</th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>10</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 3-6</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 6-12</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 12-24</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Pts With First Event in Category (n)

- Total pts with first event, n: 24
- Pts still on study, n: 131
- Pts still on treatment, n: 131

Reckamp K, et al. WCLC 2015. ORAL02.01.
Distribution of Immune-Related AEs With CTLA-4, PD-1, and PD-L1 Inhibition

Clinical Vignette

- A 72-yr-old male is treated with nivolumab on a clinical trial for metastatic HCC
- After his third cycle of treatment, he develops diarrhea, 3 times/day, treated with loperamide
- Despite conservative management, his diarrhea increases to 8 times/day
In addition to discontinuing nivolumab, which other step would you take?

A. IV hydration
B. Methylprednisolone (or equivalent)
C. Infliximab
D. Methylprednisolone (or equivalent) and infliximab
Conclusions

• Immunotherapy has emerged as an exciting therapeutic strategy
• We need to enrich the clinical experience of checkpoint inhibitors in treating malignancies
• Assessing the molecular biomarkers that are important in predicting treatment response, resistance, and treatment-related AEs
• Combination strategies to improve the efficacy of checkpoint inhibitors under investigation
• Clinicians should be vigilant in monitoring the unique AE profiles of immunotherapy
  – Close monitoring and timely management of irAEs critical
Questions?