• **Immunotherapy for Upper GI Cancers**
  – *Esophageal Adenocarcinoma*
  – *GE Junction Adeno*
  – *Gastric Carcinoma*

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Medical Director of GI Cancer Program, Florida Hospital Cancer Institute
Associate Professor University of Central Florida, College of Medicine
Esophageal Cancer: Statistics, Risk Factors

- The American Cancer Society estimates 17,290 esophageal cancer in the US for 2018:
  - 13,480 in men and 3,810 in women
  - 15,850 deaths from esophageal cancer (12,850 in men and 3,000 in women)

- Esophageal cancer is more common among men than among women. The lifetime risk of esophageal cancer in the United States is about 1 in 132 in men and about 1 in 455 in women.

- Age, Gender
- GERD
- Barrett’s Esophagus
- Tobacco and ETOH
- Obesity
- Diet
- Achalasia
- Tylosis
- HPV (Asia, South America)
Gastric Cancer in the US: 

- The ACS estimates 26240 Gastric cancer in the United States for 2018  
  - 16,520 in men and 9,720 in women  
- About 10,800 people will die of Gastric cancer 
- The risk that a man will develop Gastric cancer in their lifetime is about 1 in 95. For women the chance is about 1 in 154

STATS, Risk

- Age, Gender  
- H. Pylori  
- Tobacco Use  
- Obesity  
- Pernicious Anemia  
- Inherited Syndromes  
- Hereditary Diffuse Gastric Syndrome  
  - HNPCC/ Lynch Synd.  
  - FAP Syndrome  
  - BRCA1/BRCA2  
  - Li-Fraumeni syndrome  
  - Peutz-Jeghers syndrome (PJS)
Gastro-Esophageal Oncogenesis and Biomarkers

- CIN
  - Intestinal histology
  - TP53 mutation
  - RTK-RAS activation

- EBV
  - PIK3CA mutation
  - PD-L1/2 overexpression
  - EBV-CIMP
  - CDKN2A silencing
  - Immune cell signalling

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

- GS
  - Diffuse histology
  - CDH1, RHOA mutations
  - CLDN18-ARHGAP fusion
  - Cell adhesion

- Mutation
  - Oncogene: KRAS, PIK3CA, CTNNBB, NRAS, EBBB, ERBB4, FGFR4
  - TSGs: TP53, CDKN1A, APC, BCC, FAT1, RNF43, BUB1

- m/sRNA
  - OncomiRs: miR21, miR27a, miR130b, miR155, miR203, miR205
  - TS miRs: miR21, miR17, miR93, miR98

- Alternative splicing
  - CD44 variants, ZAF kinase, PPP1R8-B-STAT3 (read-through transcription)

- Gene fusion
  - RAF fusions: CD44-SCC122, CLDN19-ARRgap26, ROS1 fusions

- Exoenetics
  - DNA methylation: CDH1, RUNX3, p16, MLLH
  - GSEA202A, BCL2, ERBB4, CIMP-adjacent signature

- Pathways: APB-P3H2-P4-16A5 resistance signature
Gastro-Esophageal carcinoma: Biomarkers

- Somatic Mutations are highly seen in GE presenting as truncated proteins
- Increased Lymphocyte infiltration in the tissue
- Checkpoint Ligand strongly expressed: PD1, PDL-1, LAG-3 and CTLA-4
Gastric carcinoma Pathogenesis: How do we get there?
Current Status of GE Cancers: AdenoCa.

Recommendations

NCCN Guidelines 2018

Adenocarcinoma

Stage I-IIIA (locoregional disease)

- Multidisciplinary evaluation
  - Consider enteral feeding tube (jejunal or PEG tube preferred) or PEG tube for preoperative nutritional support
  - Laparoscopy (optional)
  - If no evidence of M1 disease and tumor is at esophagogastric junction (EGJ)

Medically fit for surgery

Non-surgical candidate

See ESOPH.12

See ESOPH.17

NCCN Guidelines Version 2.2018

Eosophageal and Esophagogastric Junction Cancers

PRINCIPLES OF SYSTEMIC THERAPY

Preoperative Chemoradiation

Infusional fluorouracil can be replaced with capecitabine.

Preferred Regimens
- Paclitaxel and carboplatin (category 1)
- Fluorouracil and oxaliplatin (category 1)
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)
- Miristecin and cisplatin (category 2B)
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)

Definitive Chemoradiation

Infusional fluorouracil can be replaced with capecitabine.

Preferred Regimens
- Fluorouracil and cisplatin (category 1)
- Fluorouracil and oxaliplatin (category 1)
- Paclitaxel and carboplatin

Other Recommended Regimens
- Cisplatin with docetaxel or paclitaxel
- Miristecin and cisplatin (category 2B)
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)

Postoperative Chemoradiation

- Fluoropyrimidine (infusional fluorouracil P or capecitabine)
- Before and after fluoropyrimidine-based chemoradiation

Postoperative Chemotherapy

- Capecitabine and oxaliplatin
**Approved Treatment Options for Advanced Esophageal / Gastric Cancers**

### NCCN Guidelines Version 2.2018

**Esophageal and Esophagogastric Junction Cancers**

### PRINCIPLES OF SYSTEMIC THERAPY

**Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)**

- Trastuzumab should be added to first-line chemotherapy for HER2 overexpressing metastatic adenocarcinoma

#### Combination with fluoropyrimidine and cisplatin (category 1)

- Combination with other chemotherapy agents (category 2B)
- Trastuzumab is not recommended for use with anthracyclines

### 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 evaluations.**

#### Preferred Regimens

- Fluoropyrimidine (fluorouracil® or capecitabine) and cisplatin (category 1)
- Fluoropyrimidine (fluorouracil® or capecitabine) and oxaliplatin (19,29,35)

#### Other Recommended Regimens

- Paclitaxel with cisplatin or carboplatin (14,26)
- Docetaxel with cisplatin (7,28)
- Fluoropyrimidine (10,29,33) (fluorouracil® or capecitabine)
- Docetaxel (7,35)
- Paclitaxel (23,37)
- Fluorouracil® and irinotecan (25)
- DCF modifications
  - Docetaxel, cisplatin, and fluorouracil (23,36)
  - Docetaxel, oxaliplatin, and fluorouracil (7)
  - Docetaxel, carboplatin, and fluorouracil (category 2B)
- ECS (epirubicin, cisplatin, and fluorouracil) (category 2B)
- ECS modifications (category 2B)
- Epirubicin, oxaliplatin, and fluorouracil
- Epirubicin, cisplatin, and capecitabine
- Epirubicin, oxaliplatin, and capecitabine

### Second-Line or Subsequent Therapy

- Dependent on prior therapy and PS

#### Preferred Regimens

- Ramucirumab and paclitaxel for adenocarcinoma
  - (category 1 for E.G. adenocarcinoma; category 2A for esophageal adenocarcinoma)
- Docetaxel (category 1)
- Paclitaxel (category 1)
- Irinotecan (category 1)
- Fluorouracil® and irinotecan (44,47,48)
- Pembrolizumab
- For second-line or subsequent therapy for MSI-H or dMMR tumours

#### Other Recommended Regimens

- Ramucirumab for adenocarcinoma (category 1 for E.G. adenocarcinoma; category 2A for esophageal adenocarcinoma)
- Irinotecan and cisplatin (23,26)
- Pembrolizumab
- For third-line or subsequent therapy for PD-L1 positive esophageal and E.G. adenocarcinoma
- Docetaxel and irinotecan (category 2B)

**Presented by:** [NCCN Guidelines](https://www.nccn.org/professionals/physician_gls/pdf/hscc_v2.2018.pdf)
**FLOT4 Study Design**

Randomized, multicenter, investigator-initiated, phase II/III study

- Gastric cancer or adenocarcinoma of the gastro-esophageal junction type I-III
- Medically and technically operable
- cT2-4/cN-any/cM0 or cT-any/cN+/cM0

Stratification: ECOG (0 or 1 vs. 2), location of primary (GEJ type I vs. type II/III vs. stomach), age (< 60 vs. 60-69 vs. ≥70 years) and nodal status (cN+ vs. cN-).

**FLOT x4 - RESECTION - FLOT x4**
- **FLOT**: docetaxel 50mg/m², d1; 5-FU 2600 mg/m², d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1, every two weeks

**ECF/ECX x3 - RESECTION - ECF/ECX x3**
- **ECF/ECX**: Epirubicin 50 mg/m², d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or capecitabine 1250 mg/m² p.o. divided into two doses d1-d21), every three weeks
# FLOT4: Overall Survival

![Graph showing survival probability over months for ECF/ECX and FLOT treatment groups.](image)

<table>
<thead>
<tr>
<th></th>
<th>ECF/ECX</th>
<th>FLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS months</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>[HR]</td>
<td>0.77</td>
<td>[0.63 - 0.94]</td>
</tr>
<tr>
<td>p</td>
<td>0.012</td>
<td>(log rank)</td>
</tr>
<tr>
<td>OS rate* 2y</td>
<td>59%</td>
<td>68%</td>
</tr>
<tr>
<td>OS rate* 3y</td>
<td>48%</td>
<td>57%</td>
</tr>
<tr>
<td>Projected OS rate 5y</td>
<td>36%</td>
<td>45%</td>
</tr>
</tbody>
</table>
Gastro-esophageal CA Current Status: Biomarkers/Target Rx
Gastro-esophageal CA Current Status: Biomarkers/ Combination Target Rx

- ERB/Heur-2 inhibition $\rightarrow$ PDL-1 Inhibition $\rightarrow$ Optimize ImmunoRx

- VEGF $\rightarrow$ may expert Immune suppressive effect through tissue remodeling and fibrosis $\rightarrow$ preventing immune infiltration into tumors

- Epigenetic $\rightarrow$ DNA methylation and histone modification may lead regulation of immune checkpoints and tumor antigen expression

Immunotherapy in GE cancers: Challenges and Future

- Role of Biomarkers and What constitutes PD-L1 positive staining?

- Resistance: How does resistance develop, Can we overcome the process?

- Can Immunotherapy be combined with chemotherapy for GE cancers?

- Can immunotherapy be combined to improve the likelihood of response?
Immunological “Wheel” Depicting Three “Immune Contextures” in Tumors

Immunological “Wheel” Depicting Three “Immune Contextures” in Tumors

Lack of TLS
Abundant immature DCs and lymphocytes,
Abundant M2 Macrophages
IL-1, IL-6, TNF-a, PD-L1 and PD-L2 expression

Abundant TLS associated with mature DC
Abundant CTLs and M1 Macrophages
IFN-γ and CXCL13

TLS - tertiary lymphoid structures
Blood vessel
Lymph node
Tumor

Activation/priming of T cells
- mAb against PD-1, PD-L1, CTLA-4
- IL-2
- IL-12
- Agonists for CD137, OX40, CD27

Presentation of tumor-associated antigens by APC
- Vaccines
- IFN-α
- GM-CSF

Release of tumor-associated antigens
- Chemotherapy
- Radiotherapy
- Targeted therapy

Migration of activated T cells to the tumor via blood vessels

Infiltration of T cells into the tumor
- mAb against VEGF/VEGFR

Recognition and killing of tumor cells
- mAb against PD-1, PD-L1, IDO, LAG-3

Targeting Checkpoints as an Approach to Cancer Therapy

Select Agents Targeting NK Cells (Innate Immunity)
- Lirilumab

Select Agents Targeting T Cells (Adaptive Immunity)
- MOXR0916
- TRX518
- Urelumab
- Varilumab
- Tremelimunab
- Ipilimumab
- Nivolumab
- Pembrolizumab
- Durvalumab
- Atezolizumab
- Avelumab
- BMS-986016

*CTLA-4=cytotoxic T-lymphocyte antigen-4; GITR=glucocorticoid-induced TNFR family related gene; KIR=killer-cell immunoglobulin-like receptor; LAG-3=lymphocyte-activation gene-3; NK=natural killer; PD-1=programmed death-1; PD-L1=programmed death ligand-1.
**PD-L1 Expression IHC**

- PD-L1 expression in gastric cancer is determined by combined positive score (CPS)

\[
\text{CPS} = \frac{\text{No. of PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total No. viable tumor cells}} \times 100
\]

- A specimen is considered to have positive PD-L1 expression if CPS \( \geq 1 \)

\[\text{PD-L1–negative} \quad \text{PD-L1–positive}\]
Biomarkers To Predict Response
To Immunotherapy

PD-L1
IHC

MSI, MMRd
IHC, PCR, NGS

TML/TMB*
NGS

Interferon-gamma expression signature?
Tumor Infiltrating Lymphocytes?
Qualification of Mutation/Neoantigen?

*Currently under FDA examinations.
Phase II multicenter, open-label trial of pembrolizumab as monotherapy in three different treatment-refractory patient populations

N=83

- dMMR CRC n=28
- pMMR CRC n=25
- dMMR non-CRC n=30

Pembrolizumab 10 mg/kg Q2W

- Primary Outcome Measures: irPFS*, irORR† (using irRC)
- Secondary Outcome Measures: OS, irPFS/PFS (using irRC and RECIST 1.1), ORR, IRAEs, MSI and treatment response, markers of MSI status

- dMMR and pMMR CRC groups had received a median of 3 and 4 prior treatment regimens, respectively

Phase I/II open-label study of nivolumab and nivolumab plus ipilimumab in recurrent and metastatic colon cancer: MSI-H Metastatic Colorectal Cancer

Key Inclusion Criteria
- 2nd-line, recurrent/metastatic disease
- ≥1 prior treatment for metastatic disease
- MSI-H*
- ≥1 target lesion
- ECOG PS: 0-1

Nivo mono 3mg/kg Q2W

Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg Q3W for 4 cycles†

Expansion

Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg Q3W for 4 cycles†

• **Primary Outcome Measures:** Investigator-assessed ORR by RECIST 1.1 in MSI-H patients
• **Secondary Outcome Measure:** Independent radiology review committee-assessed ORR

- 86% and 93% of patients in the Nivo mono and Nivo + Ipi groups had ≥2 prior therapy lines, respectively

*Confirmed by ≥30% of marker with instability by PCR, or by loss of ≥1 marker by immunohistochemistry. †Followed by nivo 3 mg/kg Q2W thereafter.
**MSI-high tumours are responsive to PD-1 inhibitors**

*Pembrolizumab*  
*(KEYNOTE 016, phase II)*

---

<table>
<thead>
<tr>
<th>Change from baseline SLD (%)</th>
<th>0</th>
<th>–25</th>
<th>–50</th>
<th>–75</th>
<th>–100</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR-proficient CRC</td>
<td>0</td>
<td>730</td>
<td>365</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MMR-deficient CRC</td>
<td>0</td>
<td>730</td>
<td>365</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Lynch Syndrome (yes/no/unknown): MMR-deficient CRC = 54/7/39; MMR-proficient CRC = 0/100/0*

1. Le et al. ASCO 2016;
**MSI-high tumours are responsive to PD-1 inhibitors**

**Nivolumab ± ipilimumab**

*CheckMate-142, Phase II*

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>% change truncated to 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 6 12 18 24 30 36 42 48 54 60 66 72 78 84</td>
<td>81% of patients with reduction</td>
</tr>
</tbody>
</table>

56% of patients with reduction

*Lynch Syndrome (yes/no/unknown): MMR-deficient CRC = 54/7/39; MMR-proficient CRC = 0/100/0*
## Immunotherapy in Gastric CA

<table>
<thead>
<tr>
<th>Immunotherapy</th>
<th>Target</th>
<th>Phase</th>
<th>N</th>
<th>Author</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>3</td>
<td>493</td>
<td>Kang 2017</td>
<td>mOS: 5.3 (nivo) vs 4.1 mo (placebo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR, 0.63; P&lt;0.0001</td>
</tr>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>PD-1 &amp; CTLA-4</td>
<td>1/2</td>
<td>160</td>
<td>Janjigian 2016</td>
<td>mOS: 6.9 mo (nivo 1 mg/kg + ipi 3 mg/kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.8 mo (nivo 3 mg/kg + ipi 1 mg/kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.0 mo (nivo 3 mg/kg)</td>
</tr>
<tr>
<td>Tremelimumab</td>
<td>CTLA-4</td>
<td>2</td>
<td>18</td>
<td>Ralph 2010</td>
<td>1 PR &gt;30 mo</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>Expansion</td>
<td>1</td>
<td>Tabernero 2013</td>
<td>1 pt had TTP of 9.8 mo</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>Dose-expansion</td>
<td>28</td>
<td>Segal 2014</td>
<td>2 PRs and 12-week DCR of 25%</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-1 (KEYNOTE-012)</td>
<td>1b</td>
<td>36</td>
<td>Muro 2016</td>
<td>ORR=22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>53% of pts had reduction in size of target lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median duration of response=40 wks</td>
</tr>
</tbody>
</table>
Immunotherapy in Esophagus CA

PD-L1 and PD-L2 staining is prognostic
### KEYNOTE-059 (NCT02335411): Phase 2 Multicohort Study of Pembrolizumab for G/GEJ Adenocarcinoma

<table>
<thead>
<tr>
<th>Cohort 1 Patients</th>
<th>Pembrolizumab 200 mg Q3W</th>
<th>Treat for 24 months, or until progression, intolerable toxicity, or other reason</th>
<th>Follow-up for survival by telephone until death, withdrawal, or study end</th>
</tr>
</thead>
<tbody>
<tr>
<td>- ≥2 prior lines of chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 2 Patients</td>
<td>Pembrolizumab 200 mg Q3W + cisplatin 80 mg/m² Q3W + 5-FU 800 mg/m² Q3W or capecitabine 1000 mg/m² BID Q3W&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No prior therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 3 Patients</td>
<td>Pembrolizumab 200 mg Q3W</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No prior therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- PD-L1 positive</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Response assessment by RECIST v1.1: first scan at 9 weeks after cycle 1, every 6 weeks for 1st year, followed by every 9 weeks

<sup>a</sup>Capecitabine was administered only in Japan
KEYNOTE-059 (NCT02335411): Phase 2 Multicohort Study of Pembrolizumab for G/GEJ Adenocarcinoma

Cohort 1 Patients
- ≥2 prior lines of chemotherapy

Pembrolizumab
200 mg Q3W

Cohort 2 Patients
- No prior therapy

Pembrolizumab 200 mg Q3W +
cisplatin 80 mg/m² Q3W +
5-FU 800 mg/m² Q3W or
capcitabine 1000 mg/m² BID Q3W\textsuperscript{a}

Treat for
24 months,
or until
progression,
intolerable
toxicity, or
other reason

Cohort 3 Patients
- No prior therapy
- PD-L1 positive

Pembrolizumab
200 mg Q3W

Follow-up for
survival by
telephone
until death,
withdrawal,
or study end

Response assessment by RECIST v1.1: first scan at 9 weeks after cycle 1, every 6 weeks for 1st year, followed by every 9 weeks

\textsuperscript{a}Capcitabine was administered only in Japan
KEYNOTE-059 (NCT02335411): Phase 2 Multicohort Study of Pembrolizumab for G/GEJ Adenocarcinoma

**CONCLUSION**

- Pembrolizumab monotherapy showed encouraging efficacy and manageable safety after ≥2 prior lines of therapy
  - **Overall objective response rate (ORR) was 11.2% and 15.5% in 143 PD-L1-positive patients**
  - ORR was higher in patients with PD-L1–positive tumors, but responses were also observed in patients with PD-L1–negative tumors
- Pembrolizumab plus 5-FU & cisplatin showed manageable safety and encouraging antitumor activity as first-line therapy
  - **(ORR was 60% and 68.8% in PD-L1-positive patients)**
## Response in All Patients and by PD-L1 Expression

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>PD-L1 Positive</th>
<th>PD-L1 Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 25</td>
<td>n = 16</td>
<td>n = 8</td>
</tr>
<tr>
<td>n</td>
<td>% (95% CI(^b))</td>
<td>% (95% CI(^b))</td>
<td>% (95% CI(^b))</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>15 60 (39-79)</td>
<td>11 69 (41-89)</td>
<td>3 38 (9-76)</td>
</tr>
<tr>
<td><strong>DCR(^c)</strong></td>
<td>20 80 (59-93)</td>
<td>13 81 (54-96)</td>
<td>6 75 (35-9)</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>1 4 (0-20)</td>
<td>0 0 (0-21)</td>
<td>1 13 (0-53)</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>14 56 (35-76)</td>
<td>11 69 (41-89)</td>
<td>2 25 (3-65)</td>
</tr>
</tbody>
</table>

Data cutoff: Jan 16, 2017

\(^a\)Only confirmed responses were included

\(^b\)Based on binomial exact confidence interval method

\(^c\)CR+PR+SD≥2 months
Only patients with measurable disease per RECIST v1.1 by central review at baseline and at least 1 postbaseline tumor assessment were included (n = 223)

<table>
<thead>
<tr>
<th>PD-L1 Expression</th>
<th>Patients with reduction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>42.4</td>
</tr>
<tr>
<td>PD-L1 positive</td>
<td>47.3</td>
</tr>
<tr>
<td>PD-L1 negative</td>
<td>36.7</td>
</tr>
</tbody>
</table>

Maximum Percentage Change From Baseline in Target Lesion Size

*Only patients with measurable disease per RECIST v1.1 by central review at baseline and at least 1 postbaseline tumor assessment were included (n = 223)*
Treatment Exposure\textsuperscript{a} and Duration of Response

Data cutoff: Jan 16, 2017. \textsuperscript{a}Patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥1 postbaseline assessment (n = 30). Bar length indicates time to last imaging assessment. \textsuperscript{b}no progressive disease at last disease assessment.

### Median DOR (95% CI), months

<table>
<thead>
<tr>
<th>Group</th>
<th>Median DOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>8.4 (1.6\textsuperscript{b} to 17.3+)</td>
</tr>
<tr>
<td>PD-L1 positive</td>
<td>16.3 (1.6\textsuperscript{b} to 17.3+)</td>
</tr>
<tr>
<td>PD-L1 negative</td>
<td>6.9 (2.4 to 7.0+)</td>
</tr>
</tbody>
</table>

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**Confirmed Responders (n=30)**

- CR
- PR
- Progressive disease
- Death
- Ongoing pembrolizumab treatment

---

Data cutoff: Jan 16, 2017. \textsuperscript{a}Patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥1 postbaseline assessment (n = 30). Bar length indicates time to last imaging assessment. \textsuperscript{b}no progressive disease at last disease assessment.
## Response by Line of Therapy

<table>
<thead>
<tr>
<th>Response</th>
<th>Third Line (n = 134)</th>
<th></th>
<th>Fourth+ Line (n = 125)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>95% CI</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>ORR</td>
<td>16.4</td>
<td>10.6-23.8</td>
<td>6.4</td>
<td>2.8-12.2</td>
</tr>
<tr>
<td>DCR(^b)</td>
<td>31.3</td>
<td>23.6-39.9</td>
<td>22.4</td>
<td>15.4-30.7</td>
</tr>
<tr>
<td>CR</td>
<td>3.0</td>
<td>0.8-7.5</td>
<td>1.6</td>
<td>0.2-5.7</td>
</tr>
<tr>
<td>PR</td>
<td>13.4</td>
<td>8.2-20.4</td>
<td>4.8</td>
<td>1.8-10.2</td>
</tr>
</tbody>
</table>

Data cutoff: Jan 16, 2017

\(^a\) Only confirmed responses were included

\(^b\) CR+PR+SD≥2 months
**CHECKMATE 032**: Nivolumab +/- Ipilimumab in advanced refractory G-E cancers

ASCO 2017

Nivolumab ± Ipilimumab in Patients With Advanced/Metastatic Chemotherapy-Refractory Gastric, Esophageal, or Gastroesophageal Junction Cancer: CheckMate 032 Study

Yelena Y. Janjigian,1 Patrick A. Ott,2 Emiliano Calvo,3 Joseph W. Kim,4 Paolo A. Ascierto,5 Padmanee Sharma,6 Katrina Peltola,7 Dirk Jaeger,5 Jeffrey Evans,5 Filippo de Braud,10 Ian Chau,11 Marina Tschakka,12 Christopher T. Harbison,12 Weiguang Cai,12 Johanna Bendell,13 Dung T. Le14

1Vascular Envelope Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; 2 Dana-Farber Cancer Institute, Boston, MA; 3SITEMP Madrid, Centro Integral Oncologico Clara Campoam; Madrid, Spain; 4 Yale Cancer Center, New Haven, CT; 5 Institut National du Cancer (INCa), Paris, France; 6The University of Texas MD Anderson Cancer Center, Houston, TX; 7 Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland; 8 National Cancer Institute, National Institutes of Health, Bethesda, MD; 9Black Dog Institute, Sydney, NSW, Australia; 10Fox Chase Cancer Center, Philadelphia, PA; 11Sarah Cannon Research Institute, Nashville, TN; 12Sydney, Australia; 13Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

**Checkmate 032 EG Cohort**

Western patients with advanced/metastatic EG cancer with progression on ≥1 prior chemotherapy

N = 160

**Nivolumab 3 mg/kg IV Q2W (NIVO 3)**

Median (range) follow-up (mo): 28 (17 to 35)

Primary endpoint:

- ORR per RECIST v1.1

Secondary endpoints:

- OS, PFS, TTR, DOR
- Safety

**Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg IV Q3W (NIVO 1 + IPI 3)**

Median (range) follow-up (mo): 24 (21 to 33)

**Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg IV Q3W (NIVO 3 + IPI 1)**

Median (range) follow-up (mo): 22 (19 to 25)

Primary endpoint:

- PD-L1 tumor expression (Dako 28-8 pharmDx assay)

Secondary endpoints:

- OS, PFS, TTR, DOR
- Safety
**CHECKMATE 032**: Nivolumab +/- Ipilimumab in advanced refractory G-E cancers

ASCO 2017

- **Best Reduction in Target Lesions**

  - **NIVO 3**
  - **NIVO 1 + IPI 3**
  - **NIVO 3 + IPI 1**

  - Responses were observed regardless of PD-L1 expression

- **Progression-Free Survival**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>mPFS (95% CI), months</th>
<th>6-month PFS rate, %</th>
<th>12-month PFS rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO 3</td>
<td>1.4 (1.2, 1.5)</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>NIVO 1 + IPI 3</td>
<td>1.4 (1.2, 1.3)</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>NIVO 3 + IPI 1</td>
<td>1.6 (1.4, 2.6)</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>
CONCLUSION

- Nivolumab tested in heavily pretreated patients with both PD-L1-positive and negative advanced gastric or GEJ cancer, having an ORR of 14% accompanied with an acceptable safety profile.
- PD-L1 positivity (PD-L1 expression above 1%) was associated with improved responses.
Major phase 3 trials involving targeted immunotherapeutic agents in the advanced/metastatic gastric cancer setting

<table>
<thead>
<tr>
<th>Trials</th>
<th>No. of patients</th>
<th>Treatment arms</th>
<th>HR for death ($P$ value)</th>
<th>Primary endpoint comparison (in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced gastric cancer – first line</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bang et al. 26 (ToGA)³</td>
<td>584</td>
<td>CX/CF + Trastuzumab versus CX/CF</td>
<td>0.74 (0.0046)</td>
<td>OS: 13.8 versus 11.1</td>
</tr>
<tr>
<td>Advanced gastric cancer – Second line</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fuchs et al. 32 ( REGARD)</td>
<td>355</td>
<td>Ramucirumab + BSC versus BSC</td>
<td>0.776 (0.0473)</td>
<td>OS: 5.2 versus 3.8</td>
</tr>
<tr>
<td>Wilke et al. 33 (RAINBOW)</td>
<td>665</td>
<td>Paclitaxel + Ramucirumab versus Paclitaxel</td>
<td>0.81 (0.017)</td>
<td>OS: 9.6 versus 7.4</td>
</tr>
<tr>
<td>Advanced gastric cancer – third line</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al. 34 (Apatinib)</td>
<td>271</td>
<td>Apatinib + BSC versus BSC</td>
<td>0.71 (0.0149)</td>
<td>OS: 6.5 versus 4.7PFS: 2.6 versus 1.8</td>
</tr>
<tr>
<td>Kang et al. 46 (ONO-4538-12, ATTRACTION-2)</td>
<td>493</td>
<td>Nivolumab versus Placebo</td>
<td>0.63 (&lt;0.0001)</td>
<td>OS: 5.26 versus 4.14</td>
</tr>
</tbody>
</table>
Future Status of Immunotherapy

- Immunotherapy Beyond 3rd Line RC
- Combination with Cytotoxic Agents
- Combination with Targeted Therapy: Anti-VEGF, TKI
- Immunotherapy and Radiation
- Role of Immunotherapy in Adjuvant Setting?
- Combo: Nivo + Ipilimumab
Efficacy of Nivolumab in ≥ 3rd line AGC:  Attraction-2

Presented by: Yoon Koo Kang, ASCO GI Jan 2017
Pembrolizumab vs paclitaxel for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Phase III KEYNOTE-061 Trial.

KEYNOTE-061

- Patients
  - Unresectable or metastatic gastric or GEJ adenocarcinoma
  - Progression on or after prior platinum + fluoropyrimidine chemotherapy
  - ECOG PS 0-1
  - Measurable disease
  - Availability of tumor sample for PD-L1 status

- Randomize 1:1 N ≤ 720

- Pembrolizumab 200 mg IV Q3W
  - Continued for 24 months or until progression, intolerable toxicity, or investigator or patient decision

- Paclitaxel 80 mg/m² IV days 1, 8, and 15 of 4-week cycles
  - Continued until progression, intolerable toxicity, or investigator or patient decision

Follow-up for safety (≤90 days)
Follow-up for survival (every 12 weeks)

Stratification by:
- ECOG PS (0 vs 1)
- Geographic region (Europe/Israel/North America/Australia vs East Asia vs rest of the world)
- PD-L1 expression status

Ohtsu A et al. J Clin Oncol 34, 2016 (suppl 4S; abstr TPS183)
Pembrolizumab vs paclitaxel for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Phase III KEYNOTE-061 Trial.

- Open-label, phase 3 study: Eligible patients were randomized (1:1) to receive
  - Pembrolizumab 200 mg Q3 wks for up to 2 years or standard-dose paclitaxel.
  - Primary endpoints → OS and PFS in patients with (PD-L1) combined positive score (CPS) of 1 or >. Safety was assessed in all patients, irrespective of CPS.

- 592 patients were enrolled. Of the 395 patients who had a PD-L1 CPS of 1 or higher
  - 196 patients were assigned tp Pembrolizumab Vs 199 patients were assigned to receive paclitaxel.
  - Median OS was 9·1 months (95% CI 6·2–10·7) with pembrolizumab Vs 8·3 months with paclitaxel
  - (hazard ratio 0·82, one-sided p=0·0421).
  - Median progression-free survival was 1·5 months (95% CI 1·4–2·0) with pembrolizumab and 4·1 months (3·1–4·2) with paclitaxel (HR 1·27, 95% CI 1·03–1·57).

- Conclusion:
  - Pembrolizumab did not significantly improve overall survival compared with paclitaxel as second-line therapy for advanced gastric or Gastro-Esophageal junction cancer with PD-L1 CPS of 1 or higher.
  - Pembrolizumab had a better safety profile than paclitaxel

Presented at World of GI cancer Barcelona June 2018
TRIAL DESIGN

Research Biopsy: IHC, RNA, Blood samples

Tissue retrieval exploratory biomarkers

Tissue for: IHC; RNA; DNA; FACS

Assess 24 month PFS

Maintenance pembro for 12 months total

Resectable GE junction or gastric adenocarcinoma

3 cycles Pembrolizumab & chemotherapy q21d

1 cycle Pembrolizumab q21d

Curative surgical resection

3 cycles Pembrolizumab & chemotherapy q21d

Assess path CR

Postoperative period: resume tx 6-9 weeks post op
Disease assessment q12 weeks - CT

Neoadjuvant therapy period: 12-16 weeks

CT or PET/CT and EUS for staging

Toxicity evaluation

CT for restaging

Oberstein PE et al. J Clin Oncol 36, 2018 (suppl 4S; abstr TPS197)
Phase III Trial : CheckMate 649  

Abstract 2018

- A Phase III Randomized Multicenter, open-Label in Pts with Advanced Gastric or GE Junction
- 870 pts aged ≥ 18 years with untreated advanced or metastatic G/GEJ cancer with or without PD-L1 expression will be randomized:
  - Nivo + Ipi (4 doses; followed by Nivo monotherapy) or
  - Investigator’s choice of capecitabine/oxaliplatin (XELOX) or FU /leucovorin/oxaliplatin (FOLFOX).

- Tumor tissue for determination of PD-L1 status must be provided from ≤ 6 months before study treatment.
- Pts receiving chemotherapy or radiotherapy for G/GEJ cancer within the last 6 months or pts with suspected autoimmune disease, uncontrolled medical disorder, or active infection are excluded.

- Primary endpoint is OS in pts with PD-L1+ tumors.
- Secondary endpoints is OS in all pts and progression-free survival and time to symptom deterioration in all pts and pts with PD-L1+ tumors.

Moehler M. H., Janjigian Y. Y., Adenis A., Aucoin J. S., Boku N., Chau I., et al. ASCO 2018
Radiation and Immunotherapy

- Radiation therapy interacts with the tumor and immune system through a variety of mechanisms.
  - It promotes the release of tumor neoantigens during cancer cell death,
  - Generates tumor-specific T cells with local as well as potentially distant, systemic effects.
  - Key molecular signals generated by radiation-induced cell death that promote uptake of dying cancer cells by dendritic
    - Antigen cross-presentation and activation of the inflammasome collectively constitute immunogenic cell death.
    - Complex effects on the tumor microenvironment → enhanced infiltration of activated T cells
    - Trials in solid tumors are investigating the strategy of combining immunostimulatory signals with radiation,
Radiation-immunotherapy combination can slow tumor growth for some patients with metastatic late-stage cancer

Phase II trial finds at least 30 percent of patients experienced favorable response after treatment

SAN DIEGO, September 24, 2017 – A new study involving patients with stage IV cancer finds that treatment with radiation therapy and immunotherapy can halt the growth of tumors by stimulating the body’s immune system to attack the cancer. In the phase II trial, patients with end-stage cancer that had spread to the lungs or liver demonstrated a favorable response to the combined treatment. Between 30 and 60 percent of the patients, depending on the treatment arm, found that their cancer stopped spreading. Findings will be presented today at the 59th Annual Meeting of the American Society for Radiation Oncology (ASTRO).
Esophageal Adeno/GE junction: Chemo-ImmunoRx with XRT

Giuroiu I et al. J Clin Oncol 36, 2018 (suppl 4S; abstr TPS199)
Management of AGC and GE cancers is an evolving process and shifting the Paradigm

PD-1 and PD-L1 inhibition has modest activity in GI malignancies

Hence, Combination Therapy is a reasonable future step

Patients who respond seem to have durable responses (significantly longer than typically seen with chemotherapy in the advanced setting)

Incorporating PD-1 Inhibition in early Stages (Peop & Post Op) of Gastric/GE junction cancers may be a crucial step in enhancing Cure rate in addition to Surgery

Ongoing Clinical Trials will be the answer to all Our questions
Cancer precision medicine project

Cancer detection

- Cancer screening
- Deep sequencing of cfDNA
- Cancer diagnosis
  - Exosome transcriptome HLA
  - TCR sequencing

Germline genetic variants

- Positive (20-30%)
  - Commercially available molecular targeted drugs
- Negative (10-20%)
  - Molecular targeted drug on clinical trials
  - Conventional cytotoxic drugs

Drug selection

- Actionable mutation
  - Oncoantigen vaccine
  - Neoantigen vaccine

In all cases, recurrence or metastasis is monitored by liquid biopsy

Personalized immunotherapy

- TCR-engineered adoptive therapy
- TCR sequencing
- Cloning of cancer-specific CTL