Manish A. Shah, MD – Upper GI

• Esophagus
  • Histology (squamous vs. adeno)
  • Etiology (tobacco/EtOH v HPV)

• Gastric
  • Histology (Intestinal vs. Diffuse)
  • Location (Cardia/GEJ vs Antrum)
  • Biology (MET, CDH1, others?)
  • Etiology (H. pylori related, others?)


PD-L1 expression determined by the Combined Positive Score

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

• All upper GI patients should have PD-L1 expression testing
• Validated antibody
  • 22C3 & 28-8
• Adenocarcinoma → examine CPS
• Squamous cell cancer → TPS or CPS
Metastatic Gastroesophageal Adenocarcinoma

Diagnostic Workup:
- Disease stage confirmed: Unresectable, metastatic, or stage IV
- Histology confirmed: Esophageal, GEJ, or gastric adenocarcinoma
- Tissue-based biomarkers obtained: NGS (including MSI and TMB*), PD-L1 CPS, and HER2 expression
- Patient considered for available clinical trials
- Immunotherapy-naive†

MSI-H or dMMR?

No

HER2 Testing

HER2-positive

Pembrolizumab + Chemotherapy + trastuzumab

Disease progression

Pembrolizumab + Chemotherapy (esophageal and Siewert type 1 GEJ)

HER2-negative

PD-L1 expression

CPS ≥5

Nivolumab + Chemotherapy

CPS <5

Chemotherapy

CPS ≥10

Chemotherapy

CPS <5

Chemotherapy®

Yes

Chemotherapy eligible

Chemotherapy ineligible

Consider anti-PD-1 ICI
Metastatic Esophageal Squamous Cell Cancer

Diagnostic Workup:
- Disease stage confirmed: Unresectable, metastatic, or stage IV
- Histology confirmed: Esophageal SCC
- Tissue-based biomarkers obtained: NGS (including MSI* and TMB†) and PD-L1 score (22C-8 TPS assay or 22C-3 CPS assay)
- Patient considered for available clinical trials
- Immunotherapy-naïve§

PD-L1 expression

Positive

CPS ≥10

First-line:
- Pembrolizumab + chemotherapy
Second-line (ICI-naïve):
- Nivolumab
- Pembrolizumab
- Chemotherapy

Chemotherapy eligible

First-line:
- Nivolumab + chemotherapy
Second-line (ICI-naïve):
- Nivolumab
- Pembrolizumab
- Chemotherapy

Chemotherapy ineligible

First-line:
- Nivolumab + ipilimumab
Second-line (ICI-naïve):
- Nivolumab
- Pembrolizumab

Negative
Other Key points

• Chemo + immune checkpoint blockade is now a standard option for most patients with upper GI cancers for CPS > 5
  • Relative autoimmune contraindications

• In general, single agent checkpoint inhibition is not recommended (outside of MMR deficient adenocarcinoma)

• Limited data in locally advanced disease
  • Perhaps better response, but survival data not available
Incidence of Mutations in Targetable Pathways in Biliary Cancers

<table>
<thead>
<tr>
<th>CGP Findings</th>
<th>IHCCA</th>
<th>EHCCA</th>
<th>GBCA</th>
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<tbody>
<tr>
<td>Total GA per patient</td>
<td>3.6</td>
<td>4.4</td>
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<tr>
<td>CRGA per patient</td>
<td>2.0</td>
<td>2.1</td>
<td>2.0</td>
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<td>ERBB2 amplifications</td>
<td>4%</td>
<td><strong>11%</strong></td>
<td><strong>16%</strong></td>
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<td>BRAF substitutions</td>
<td><strong>5%</strong></td>
<td><strong>3%</strong></td>
<td><strong>1%</strong></td>
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<tr>
<td>KRAS substitutions</td>
<td>22%</td>
<td>42%</td>
<td>11%</td>
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<tr>
<td>PI3KCA substitutions</td>
<td>5%</td>
<td>7%</td>
<td><strong>14%</strong></td>
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<tr>
<td>FGFR1-3 fusions and amplifications</td>
<td><strong>11%</strong></td>
<td>0 %</td>
<td><strong>3%</strong></td>
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<td>CDKN2A/B loss</td>
<td>27%</td>
<td>17%</td>
<td>19%</td>
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<tr>
<td>IDH1/2 substitutions</td>
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<td>0 %</td>
<td>0 %</td>
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<tr>
<td>ARID1A alterations</td>
<td>18%</td>
<td>12%</td>
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<tr>
<td>MET amplifications</td>
<td>2%</td>
<td>0 %</td>
<td>1%</td>
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Topaz-1 Trial – Gem/Cis/ Durvalumab

Key eligibility
- Locally advanced or metastatic BTC (ICC, ECC, GBC)
- Previously untreated if unresectable or metastatic at initial diagnosis
- Recurrent disease >6 months after curative surgery or adjuvant therapy
- ECOG PS 0 or 1

Stratification factors
- Disease status
  - Initially unresectable versus recurrent
- Primary tumor location
  - ICC versus ECC versus GBC

R (1:1) (N=685)

Durvalumab 1500 mg Q3W plus GemCis (up to 8 cycles)

Placebo Q3W plus GemCis (up to 8 cycles)

Durvalumab 1500 mg Q4W until PD

Placebo Q4W until PD

Primary objective
- Overall survival

Key secondary objectives
- Progression-free survival
- Objective response rate
- Duration of response
- Efficacy by PD-L1 status
- Safety
Gem/Cis /Durva improves Overall Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Overall Survival, mo (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Stratified Log-rank P Value</th>
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</thead>
<tbody>
<tr>
<td>Durva + Gem + Cis (n=341)</td>
<td>12.8 (11.1–14.0)</td>
<td>0.80 (0.66–0.97)</td>
<td>0.021</td>
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<tr>
<td>Placebo + Gem + Cis (n=344)</td>
<td>11.5 (10.1–12.5)</td>
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</table>

Oh DY et al. NEJM Evid 2022;1(8):1-11
Summary Recommendations

• Untreated, advanced biliary tract cancers should receive gemcitabine/ cisplatin/ durvalumab.

• Previously treated BTC
  • Could consider Lenvatinib + pembrolizumab
  • Nivolumab with or without ipilimumab