Recent Advances in Gastrointestinal Cancers

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Abramson Cancer Center

PENN 2016 Updates in Oncology
June 23, 2016
Disclosures

• none
ASCO 2016 Highlights:

- Practice Change 2016
- Practice Change 2017
- Practice Consideration
- Expansion of MSI deficient histologies
- Immunotherapy Potential in Rare but Real Cancer
ASCO 2016 Highlights:

• Practice Change 2016
  – ESPAC 4 - adjuvant GEM CAP
• Practice Change 2017
• Practice Consideration
• Expansion of MSI H deficient histologies
• Immunotherapy Potential in Rare but Real Cancer
ESPAC-4: A multicenter, international, open label randomized controlled phase III trial of adjuvant combination chemotherapy of gemcitabine (GEM) and capecitabine (CAP), versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma


NCRI Pancreatic Cancer Sub-Group
CRUK Liverpool Cancer Trials Unit

EudraCT#: 2007-004299-38
ISRCTN#: 43482138
CRUK#: C245/A8968/A20830

ASCO, Chicago 06/06/2016 8:00 AM - 11:00 AM LBA4006
**ESPA - 4**

722 patients pancreatic ductal adenocarcinoma ‘curative’ resection ≤12 wks

**RANDOMISATION at Liverpool Cancer Trials Unit**

- **GEMCITABINE**
  - 1000mg/m² - Days 1, 8 and 15 for 6 cycles
- **GEMCITABINE**
  - 1660mg/m²/day – 21/28d i.e. 24 weeks

**3-MONTHLY FOLLOW UP FROM RANDOMISATION TO DEATH**

Stratified log-rank test with 5% 2-sided α, for a 10% difference in 2 year survival, 90% power = 480 events = 722 patients, 361 in @ arm

<table>
<thead>
<tr>
<th>Target number of patients</th>
<th>722</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start date</td>
<td>13/01/08</td>
</tr>
<tr>
<td>Number of sites opened</td>
<td>106</td>
</tr>
<tr>
<td>Planned close date</td>
<td>01/11/14</td>
</tr>
<tr>
<td>Target achieved</td>
<td>31/07/14</td>
</tr>
</tbody>
</table>

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LCTU
Liverpool Clinical Trials Unit

NCRI
National Cancer Research Institute

UKCRC
Registered Clinical Trials Unit

NHS
National Institute for Health Research

Cancer Research UK

Presented By John Neoptolemos at 2016 ASCO Annual Meeting
# Tumour Pathology

<table>
<thead>
<tr>
<th>Stratification factors:</th>
<th>GEM (n=366)</th>
<th>GEMCAP (n=364)</th>
<th>TOTAL (n=730)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R0</td>
<td>147 (40%)</td>
<td>143 (39%)</td>
<td>290 (40%)</td>
</tr>
<tr>
<td>R1</td>
<td>219 (60%)</td>
<td>221 (61%)</td>
<td>440 (60%)</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>280 (77%)</td>
<td>276 (76%)</td>
<td>556 (76%)</td>
</tr>
<tr>
<td>FR/GER/SWE</td>
<td>86 (23%)</td>
<td>88 (24%)</td>
<td>174 (24%)</td>
</tr>
<tr>
<td><strong>Max Tumour Size (mm)</strong></td>
<td>30 (0-110)</td>
<td>30 (6-105)</td>
<td>30 (0-110)</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>30 (8%)</td>
<td>32 (9%)</td>
<td>62 (9%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>192 (52%)</td>
<td>175 (48%)</td>
<td>367 (50%)</td>
</tr>
<tr>
<td>Poor</td>
<td>140 (38%)</td>
<td>147 (40%)</td>
<td>287 (39%)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>2 (1%)</td>
<td>2 (1%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1%)</td>
<td>8 (2%)</td>
<td>10 (1%)</td>
</tr>
<tr>
<td><strong>Nodes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>67 (18%)</td>
<td>76 (21%)</td>
<td>143 (20%)</td>
</tr>
<tr>
<td>Positive</td>
<td>299 (82%)</td>
<td>288 (79%)</td>
<td>587 (80%)</td>
</tr>
</tbody>
</table>

* Median (Range)

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Presented By John Neoptolemos at 2016 ASCO Annual Meeting
## Reported Toxicity

Number of patients in Safety Set with at least one NCI CTC v4 grade 3/4 event

<table>
<thead>
<tr>
<th>CTC 3/4 event</th>
<th>GEM</th>
<th>GEMCAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>P-value*</td>
</tr>
<tr>
<td></td>
<td>(% of 366)</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>14 (4%)</td>
<td>0.279</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6 (2%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (5%)</td>
<td>0.870</td>
</tr>
<tr>
<td>Fever</td>
<td>6 (2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Infection and infestations, Other</td>
<td>24 (7%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>11 (3%)</td>
<td>0.821</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>89 (24%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hand-Foot syndrome</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelets</td>
<td>7 (2%)</td>
<td>0.800</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>9 (2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>WBC</td>
<td>28 (8%)</td>
<td>0.242</td>
</tr>
</tbody>
</table>

* Exploratory analysis: Fisher’s exact test
## ESPAC Trials: 5 Year Overall Survival

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>No. of pts (N=2092)</th>
<th>5-Year OS (95% CI)</th>
<th>Stratified Log-Rank $\chi^2$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESPAC-1</td>
<td>5FU/FA</td>
<td>149</td>
<td>21 (14.6 – 28.5) %</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No chemotherapy</td>
<td>143</td>
<td>8.0 (3.8 – 14.1) %</td>
<td>7.03</td>
<td>0.030*</td>
</tr>
<tr>
<td></td>
<td>Chemoradiotherapy (5FU/Rad)</td>
<td>145</td>
<td>10.8 (6.1 – 17.0) %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESPAC-3</td>
<td>GEM</td>
<td>539</td>
<td>17.5 (14.0 – 21.2) %</td>
<td>0.74</td>
<td>0.390*</td>
</tr>
<tr>
<td></td>
<td>5FU/FA</td>
<td>551</td>
<td>15.9 (12.7 – 19.4) %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESPAC-4</td>
<td>GEM</td>
<td>366</td>
<td>16.3 (10.2 – 23.7) %</td>
<td>4.61</td>
<td>0.032†</td>
</tr>
<tr>
<td></td>
<td>GEMCAP</td>
<td>364</td>
<td>28.8 (22.9 – 35.2) %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Stratification factor: resection margin status; †stratification factors: resection margin status and country
ESPAC 4 Conclusions

• Median survival better with GEMCAP
  – 28 months vs 25.5 months

• 5 year Overall Survival favored GEMCAP over GEM
  – 28.8 months vs 16.3 months

• Acceptable toxicity profile
ESPAC 4 Conclusions

• Combination cytotoxic chemotherapy is now a standard
• Await results of APACT and PRODIGE
• GemCap control arm for future adjuvant therapy trials?
• New adjuvant standard of care for resected pancreas cancer
ASCO 2016 Highlights:

- Practice Change 2016
- Practice Change 2017
  - Netter-1 Phase III PRRT for midgut NET
- Practice Consideration
- Expansion of MSI H histologies
- Immunotherapy Potential in Rare but Real Cancer
NETTER-1 Phase III: Progression-Free Survival, Radiographic Response and Preliminary Overall Survival Results in Patients with Midgut Neuroendocrine Tumors Treated with 177Lu-Dotatate

Jonathan Strosberg, Edward Wolin, Beth Chasen, Matthew Kulke, David Bushnell, Martyn Caplin, Richard P. Baum, Pamela Kunz, Timothy Hobday, Andrew Hendifar, Kjell Oberg, Maribel Lopera Sierra, Dik Kwekkeboom, Philippe Ruszniewski and Eric Krenning on behalf of the NETTER-1 study group.

Presented By Jonathan Strosberg at 2016 ASCO Annual Meeting
Midgut Carcinoid Tumors

- Limited therapeutic options for carcinoid tumors (midgut – 25-40% of all NET)
- Somatostatin Analogs
- Everolimus – Radiant 4
- PRRT extensive experience in Europe
What is PRRT

- Peptide Receptor Radionuclide Therapy
- Cell targeting peptide (Octreotide) is combined with radionuclide (Lu 177 or Y90)
- Octreotide + Radionuclide = Radiopeptide
- Radiopeptide injected into bloodstream
- Binds to neuroendocrine tumor cells
- Delivers high dose radiation to the NET
NETTER -1 Study Objectives and Design

**Aim**
Evaluate the efficacy and safety of $^{177}$Lu-Dotatate + SSAs (symptoms control) compared to Octreotide LAR 60mg (off-label use)$^1$ in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30mg (label use).

**Design**

**Treatment and Assessments**
Progression free survival (RECIST criteria) every 12 weeks

- Baseline and Randomization
  - $n = 115$
  - 4 administrations of 7.4 GBq of $^{177}$Lu-Dotatate every 8 weeks + SSAs (symptoms control)

- $n = 115$
  - Octreotide LAR (high dose - 60mg every 4 weeks)$^1$

$^1$ FDA and EMA recommendation
Main Inclusion Criteria

- Patients ≥18 years of age
- Metastatic or locally advanced, inoperable, histologically proven, midgut NET
- Ki67 index ≤ 20% (Grade 1-2)
- Progressive disease (RECIST Criteria 1.1 centrally confirmed) on uninterrupted fixed dose of octreotide LAR (20-30 mg every 3-4 weeks)
- Somatostatin receptor positive disease
- Karnofsky Performance Score ≥ 60
- Including functioning and non-functioning
### Objective Responses
Currently evaluable patients

<table>
<thead>
<tr>
<th></th>
<th>177-Lu-Dotatate (n=101)</th>
<th>Octreotide LAR 60 mg (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (n)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response (n)</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Objective Response Rate (*)</td>
<td>18%</td>
<td>3%</td>
</tr>
<tr>
<td>Confidence Interval (95%)</td>
<td>10% - 25%</td>
<td>0% - 6%</td>
</tr>
<tr>
<td>Statistical Significance</td>
<td></td>
<td>p = 0.0008</td>
</tr>
<tr>
<td>All patients</td>
<td>(n=116)</td>
<td>(n=113)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>6 (5%)</td>
<td>27 (24%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>77 (66%)</td>
<td>70 (62%)</td>
</tr>
</tbody>
</table>

(*) Exclude patients with no post-baseline scans or central response available
Netter-1 Conclusions

• Significant increase in PFS – not yet reached for 177-LU-Dotatate vs 8.4 months for Octreotide
• ORR 18% vs 3%
• Interim Analysis suggests OS benefit
• Safety profile favorable
• At FDA now
• Penn 2017
Role of PRRT in metastatic midgut NET

**NETTER-1:** N=316; ITT=229; 87 (27.5%) failed the screening procedures. Reasons: ? Competing treatment ? Renal function

Subsequent treatment after PRRT

**PRRT**

**Treatment modality**

- **Foregut**
  - Thymus
  - Esophagus
  - Lung
  - Stomach
  - Duodenum
  - Pancreas

- **Midgut**
  - Appendix
  - Ileum
  - Cecum
  - Ascending colon

- **Hindgut**
  - Distal large bowel
  - Rectum

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**Natural history of midgut NET (years)***

- **Surgery**
- **Somatostatin/IFN**
- **Everolimus**
- **Observation**
- **TACE/RFA/SIRT-Y90**

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*At diagnosis of metastases >5 years*

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*Presented By Stephen Chan at 2016 ASCO Annual Meeting"
ASCO 2016 Highlights:

- Practice Change 2016
- Practice Change 2017
- Practice Consideration
  - CALGB/SWOG 80405
- Expansion of MSI deficient histologies
- Immunotherapy Potential in Rare but Real Cancer
Impact of primary tumor location on Overall Survival and Progression Free Survival in patients with metastatic colorectal cancer: Analysis of CALGB/SWOG 80405 (Alliance)

CALGB/SWOG 80405

ESMO, SEP, 2014

1ST LINE MET / ADVANCED COLORECTAL

FOLFIRI or FOLFOX

CONCLUSION: NO DIFFERENCE

Chemo + Cetuximab
OS = 32.0 mos
PFS = 11.4 mos

Chemo + Bevacizumab
OS = 31.2 mos
PFS = 11.3 mos

All RAS wt
MD choice

N = 526

OS better than anticipated in both arms:
Treatment effect and/or Patient selection

Presented By Alan Venook at 2016 ASCO Annual Meeting
Metastatic Colorectal Cancer: Patient Selection

- KRAS, Any RAS mutations
- BRAF mut
- Hypermethylation
- Clinical outlier: Women, peritoneal

6 FEET OF BIOLOGICALLY COMPLEX TUBING
Right-sided primaries are more often associated with:

- Older age at diagnosis
- Female patients
- Later onset of symptoms, occult bleeding
- Flat sessile polyps
- High grade of differentiation
- Signet-ring cell / mucinous histology
- Peritoneal metastases
Embryology: The origin of the colon

Diagram showing the development of the colon and related structures, including the pharyngeal pouches, Rathke's pouch, lung bud, liver, gallbladder, ventral pancreatic bud, yolk sac (vitelline duct), cecal bud, allantois, and cloaca. The colon is divided into right and left sections.

Presented by Alan Venook at the 2016 ASCO Annual Meeting.
80405: Side of Primary Tumors

TRANSVERSE  N = 66

RIGHT  
N = 293  
(27%)

COULD NOT DETERMINE  
N = 46

LEFT  
N = 732  
(68%)
80405: Overall Survival by Sidedness

Presented By Alan Venook at 2016 ASCO Annual Meeting

<table>
<thead>
<tr>
<th>Side</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>732 (550)</td>
<td>33.3 (31.4-35.7)</td>
<td>1.55 (1.32-1.82)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Right</td>
<td>293 (242)</td>
<td>19.4 (16.7-23.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% Event Free

Months From Study Entry

Presented By Alan Venook at 2016 ASCO Annual Meeting
80405: OS by Sidedness (Bevacizumab)

**Table:**

<table>
<thead>
<tr>
<th>Side</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>356 (280)</td>
<td>31.4 (28.3-33.6)</td>
<td>1.32 (1.05-1.65)</td>
<td>0.01</td>
</tr>
<tr>
<td>Right</td>
<td>150 (121)</td>
<td>24.2 (17.9-30.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Graph:**

- % Event Free vs. Months From Study Entry
- Two lines representing Left and Right sidedness.
80405: OS by Sidedness (Cetuximab)

<table>
<thead>
<tr>
<th>Side</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>376 (270)</td>
<td>36.0 (32.6-40.3)</td>
<td>1.87 (1.48-2.32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Right</td>
<td>143 (121)</td>
<td>16.7 (13.1-19.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 80405: Sidedness is Prognostic Overall Survival (OS)

<table>
<thead>
<tr>
<th>KRAS wt N = 1025</th>
<th>Right 1° Median OS (mos)</th>
<th>Left 1° Median OS (mos)</th>
<th>Hazard Ratio 95% CI (adjusted*)</th>
<th>P (adjusted*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>19.4</td>
<td>33.3</td>
<td>1.55 (1.32, 1.82)</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Cet</td>
<td>16.7</td>
<td>36.0</td>
<td>1.87 (1.48, 2.32)</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Bev</td>
<td>24.2</td>
<td>31.4</td>
<td>1.32 (1.05, 1.65)</td>
<td>P = 0.01</td>
</tr>
</tbody>
</table>

**19.3 MONTHS IS A BIG DIFFERENCE!!**

*Adjusted for biologic, protocol chemotherapy, prior adjuvant therapy, prior RT, age, sex, synchronous disease, in place primary, liver metastases*
80405: Overall Survival by Sidedness and Biologic

- **Left/Bev**
  - Median (95%CI): 31.4 (28.3-33.6)

- **Left/Cet**
  - Median (95%CI): 36.0 (32.6-40.3)

- **Right/Bev**
  - Median (95%CI): 24.2 (17.9-30.3)

- **Right/Cet**
  - Median (95%CI): 16.7 (13.1-19.4)
**Venook et al: Major findings**

**CALGB/SWOG 80405:**
**MEDIAN OVERALL SURVIVAL BY SIDE**

<table>
<thead>
<tr>
<th>KRAS wt N = 1025</th>
<th>Right 1° Median OS (mos)</th>
<th>Left 1° Median OS (mos)</th>
<th>Adjusted Hazard Ratio</th>
<th>Log Rank P (adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>19.4</td>
<td>33.3</td>
<td>1.55</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Cetux</td>
<td>16.7</td>
<td>36.0</td>
<td>1.87</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Bev</td>
<td>24.2</td>
<td>31.4</td>
<td>1.32</td>
<td>P = 0.01</td>
</tr>
</tbody>
</table>

**BIOLOGIC BY SIDE INTERACTION**

<table>
<thead>
<tr>
<th>BIOLOGIC</th>
<th>SIDE OF PRIMARY</th>
<th>LOG RANK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any biologic OS and PFS</td>
<td>Cetux v Bev; left</td>
<td>P_{int} = 0.005</td>
</tr>
<tr>
<td>Cetux v Bev OS superiority</td>
<td>Left</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>Cetux v Bev OS superiority</td>
<td>Right</td>
<td>p = 0.08</td>
</tr>
</tbody>
</table>

**Prognostic**

**Predictive**
Sidedness = Biological Surrogate

- BRAF mutations right sided – not enough to explain
- Transcriptional Subtypes
- Hypermethylation
- Immunological Effects
- Environment (microbiome) - fusobacterium
80405: Exploratory Analysis ($wt$ v $mut$)

If true, we know less about RAS than we think we do

<table>
<thead>
<tr>
<th></th>
<th>Right 1° Median OS (mos)</th>
<th>Left 1° Median OS (mos)</th>
<th>Log Rank p (adjusted*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>19.4</td>
<td>33.3</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>KRAS $wt$ N=1025</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cet</td>
<td><strong>16.7</strong> YES</td>
<td>36.0</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>Bev</td>
<td>24.2</td>
<td>31.4</td>
<td>$P = 0.01$</td>
</tr>
<tr>
<td>All pts</td>
<td>23.1</td>
<td>30.3</td>
<td></td>
</tr>
<tr>
<td>KRAS $mut$ N=213 *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cet</td>
<td><strong>23.3</strong> NO</td>
<td>27.9</td>
<td></td>
</tr>
<tr>
<td>Bev</td>
<td>23.0</td>
<td>31.1</td>
<td></td>
</tr>
</tbody>
</table>

* pre-amendment cohort
More than two sides to this story

Age
PS
Stage

RAS
BRAF
MSI
SIDE

Presented by Kimmie Ng, MD, MPH

Presented at: ASCO Annual Meeting '16
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Sidedness in mCRC

- Sidedness is a surrogate for tumor biology
- Side of origin matters
- Right or left side is effectively a biomarker
- Clinical trials need to stratify
  - Right or Left
80405 Sidedness Take Home

- Data supports bevacizumab for frontline therapy of metastatic colorectal cancer patients with right sided tumors regardless of kras status
ASCO 2016 Highlights:

- Practice Change 2016
- Practice Change 2017
- Practice Consideration
- Expansion of MSI deficient histologies
- Immunotherapy Potential in Rare but Real Cancer
PD-1 Blockade in Mismatch Repair Deficient Cancer Independent of Tumor Histology


The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
Ohio State University Comprehensive Cancer Center, Columbus, OH
Providence Cancer Center, Portland, OR
Stanford University School of Medicine, Stanford, CA
University of Pittsburgh, Pittsburgh, PA
National Cancer Institute, Bethesda, MD
Merck & Co., Inc., Kenilworth, NJ
Mismatch Repair Deficiency

**Microsatellite instability** in tumor cells is due to deficient DNA mismatch repair:

- **germline** (Lynch syndrome) and/or **sporadic** mutations (MLH1, MSH2, MSH6, PMS2, EpCAM)
- **epigenetic silencing** (MLH1 hyper-methylation)

First defined by Papadopoulos and Vogelstein in early 1990s.
Associated tumor types

**Colorectal cancer**
- Associated with hereditary nonpolyposis colorectal carcinoma (HNPCC)
- 15% of sporadic colorectal carcinomas (3-5% of advanced disease)
- stage II CRC: associated with better prognosis, no benefit from 5FU alone
- stage IV CRC: associated with worse prognosis

**Other tumor types:**
Endometrial, gastric, small bowel, ampullary, cholangiocarcinoma, pancreatic, sarcoma, prostate, gliomas and others at similar frequencies.
Study Design

Colorectal Cancers

- Cohort A: Deficient in Mismatch Repair (n=25)
- Cohort B: Proficient in Mismatch Repair (n=25)

Non-Colorectal Cancers

- Cohort C: Deficient in Mismatch Repair (n=21)

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Primary endpoint: immune-related 20-week PFS rate and response rate
- Mismatch repair testing using standard PCR-based test for detection of microsatellite instability
Biochemical Responses

![Graph showing biochemical responses over time for MMR-proficient CRC, MMR-deficient CRC, and MMR-deficient non-CRC.](Slide10.png)
Duration of Disease Control

- MMR-proficient CRC
- MMR-deficient CRC
- MMR-deficient non-CRC

%Change from Baseline SLD

Days

REISTIC Responses

Months

dMMR non-CRC

dMMR CRC
Clinical responses in different MMR deficient tumors
Conclusions: Beyond Histology

- MMR deficient tumors across different histologies responsive
- Testing for MSI is accessible and available
- Results for MSI-H patients (CRC and non colorectal) are impressive and durable
- Select patients for immunotherapy based on molecular defect regardless of tissue of origin
ASCO 2016 Highlights:

- Practice Change 2016
- Practice Change 2017
- Practice Consideration
- Practice Status Quo
- Expansion of MSI H opportunities
- Immunotherapy Potential in Rare but Real Cancer
  - Anal Squamous Cell Carcinoma and Nivolumab
NCI9673: A Multi-Institutional ETCTN Phase II Study of Nivolumab in Refractory Metastatic Squamous Cell Carcinoma of the Anal Canal (SCCA)

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SCC of Anal Canal

• 2016:
  – 8,080 new diagnoses in US
  – 1,080 deaths
  – 27,000 new cases annually worldwide

• No established standard of care in metastatic setting

• NCCN – cisplatin-based chemotherapy
Rationale for Nivolumab in Metastatic SCCA:

- Approximately 80-95% of cases are linked to human papillomavirus (HPV).

- The role of HPV in the tumorigenesis of SCCA provides rationale for the use of immune checkpoint blockade agents as a novel therapy for treatment of patients with a virally driven disease.
Anal SCC and Nivolumab

• First prospective Phase II study completed in metastatic refractory setting
• Single agent Nivolumab well tolerated
• No SAEs in HIV + patients
• Met primary endpoint of response
• Response rate of 24% - 37 ITT
• 34 evaluable patients: 7 PR and 2 CR
GI 2016
Thematic Questions Remain

• How will further subtyping of tumors allow for personalized selection of therapies?

• What role will immunotherapy play in the management of gastrointestinal cancers?