Immunotherapy of Colorectal Cancer
(and other Gastro-intestinal track tumors)

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Immunotherapy of colorectal cancer

• As in many other tumor types
  – Colorectal cancer is extensively tested in immunotherapy
  – So far, none of the clinical trials have reached their endpoint
    • Ag-specific Monoclonal antibodies
    • Cancer vaccines
    • Adoptive cell therapies
    • Oncolytic virus immunotherapies
    • Cytokines
  – Some promising results have been obtained but,
  – No drug has been approved for CRC Immunotherapy
  – Recent data has emerged with Immune checkpoint inhibitors
KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1+ Advanced Solid Tumors

**Response assessment:** Every 8 weeks for the first 6 months; every 12 weeks thereafter

**Primary end points:** ORR per RECIST v1.1

**Secondary end points:** PFS, OS, duration of response, and safety
PD-L1 staining selection

Analysis of PD-L1 Expression

- Tumor samples: archival or newly obtained core or excisional biopsy of nonirradiated lesion
- Immunohistochemistry: assessed at a central laboratory using a prototype assay (QualTek) and 22C3 antibody clone (Merck)
- Positivity: membranous PD-L1 expression in ≥1% of cells in tumor and stroma

Examples of PD-L1 Staining in Colorectal Adenocarcinoma

Keynote 028: 137 CRC screened, 33 PD-L1 + (24%), 23 treated

O’Neil B ECCO/ESMO 2015
Keynote 028: results

Low activity of anti PD-1 Pembrolizumab in PD-L1 + mCRC

MMR deficient patient
KEYNOTE-028 phase 1b
Pembrolizumab & Biliary tract cancer

89 Screened patients

37 (41%) PDL1 +

24 treated

Pembrolizumab (10 mg/kg IV Q 2w)

- 20 Biliary tract
- 4 Gall bladder

All pre-treated:
1 line: 21%
2 lines: 42%
3 lines: 33%
4 lines: 4%
KEYNOTE-028 phase 1b
Pembrolizumab & Biliary tract cancer

Response:
- 17.4% (n=4)
- Median DoR not reached

Summary:
- Signal of efficacy of Pembrolizumab in Biliary tract tumors
- On going trial: phase I- II Pembro + FOLFOX

Bang YJ et al. - ESMO® 2015 - Abs. 525
Colorectal Cancer

Micro-satellite Instability MSI
Mismatch Repair (MMR) mechanisms

Microsatellite instability high (MSI-H) or Mismatch Repair Deficient (dMMR) colorectal carcinoma (CRC).

MSI, a form of genomic instability, occurs through the insertion or deletion of repeating nucleotides during DNA replication and failure of the mismatch repair system to correct errors in nucleotide repeat markers.

Patients with functional MMR mechanism are MSS or pMMR.
# MSI-H tumors have less metastases

<table>
<thead>
<tr>
<th></th>
<th>MSS</th>
<th>MSI-H</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td><strong>UICC stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>146 (18,2)</td>
<td>13 (14,6)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>II</td>
<td>204 (25,4)</td>
<td>42 (47,2)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>237 (29,4)</td>
<td>27 (30,3)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>217 (27,9)</td>
<td>7 (7,9)</td>
<td></td>
</tr>
<tr>
<td><strong>lymphnode metastases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>423 (52,6)</td>
<td>33 (37,1)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>no</td>
<td>381 (47,4)</td>
<td>56 (62,9)</td>
<td></td>
</tr>
<tr>
<td><strong>distant Metastases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>217 (27,0)</td>
<td>7 (7,9)</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>no</td>
<td>587 (73,0)</td>
<td>82 (92,1)</td>
<td></td>
</tr>
</tbody>
</table>

Microsatellite instability phenotype

- **Molecular testing**: Genotyping 5 microsatellites
  - MSI-H when $\geq 2$ loci were present among the 5 analyzed microsatellite loci (NR-21, BAT-26, BAT-25, NR-24 and MONO-27) detected by polymerase chain reaction (PCR)
  - If at least 2 of the 5 microsatellites are unstable, the tumor phenotype is “**MSI-high**” or dMMR

- **Immunohistochemical testing**: Expression of DNA mismatch repair protein MLH1, MSH2, MSH6 or PMS1/PMS2.
  - Loss of expression indicates that the corresponding gene is not being appropriately expressed and suggests the existence of a mutation or epigenetic silencing
Microsatellite instability phenotype

Nucleotides added repetitions

IHC Expression

MLH1 loss

MSH2 +

MSH6 +

PMS2 loss

Geiersbach KB, Samowitz WS. Arch Pathol Lab Med 2011;135:1269-77
Defective Mismatch Repair As a Predictive Marker for Lack of Efficacy of Fluorouracil-Based Adjuvant Therapy in Colon Cancer

Dan Sargent et al, JCO 2010
Colorectal Cancer

Recent classification according to biomarkers
<table>
<thead>
<tr>
<th>CMS1</th>
<th>CMS2</th>
<th>CMS3</th>
<th>CMS4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI immune</td>
<td>Canonical</td>
<td>Metabolic</td>
<td>Mesenchymal</td>
</tr>
<tr>
<td>14%</td>
<td>37%</td>
<td>13%</td>
<td>23%</td>
</tr>
</tbody>
</table>

- **CMS1 (MSI immune)**: MSI, CIMP high, hypermutation
- **CMS2 (Canonical)**: SCNA high
- **CMS3 (Metabolic)**: Mixed MSI status, SCNA low, CIMP low
- **CMS4 (Mesenchymal)**: SCNA high

**BRAF mutations**
- Immune infiltration and activation
- WNT and MYC activation
- Metabolic deregulation
- Worse survival after relapse

**KRAS mutations**
- Stromal infiltration, TGF-β activation, angiogenesis
- Worse relapse-free and overall survival

**Figure 5** Proposed taxonomy of colorectal cancer, reflecting significant biological differences in the gene expression-based molecular subtypes. CIMP, CpG island methylator phenotype; MSI, microsatellite instability; SCNA, somatic copy number alterations.

Overall Survival (n=2,796)

Overall logrank  \( p = 0.00124^* \)

CMS4 vs. CMS2

\[ HR = 1.7 (1.3 - 2.3) \]
\[ p = 0.0004^* \]

* Adjusted for stage, MSI, BRAF mut, adjuvant chemotherapy, and stratified by dataset.

Presented by: Rodrigo Dienstmann on behalf of the CRC Subtyping Consortium
Relapse-free Survival (n=2,252)

Overall logrank  \( p = 0.0018^* \)

**CMS4 vs. CMS1**

HR = 1.8 (1.1 – 2.9)

\( p = 0.01^* \)

**CMS4 vs. CMS2**

HR = 1.6 (1.2 – 2.0)

\( p = 0.0006^* \)

* Adjusted for stage, MSI, BRAF mut, adjuvant chemotherapy, and stratified by dataset.
Survival after relapse (n=593)

Overall logrank  \( p = 0.0004^* \)

CMS1 vs. CMS2
\[ HR = 2.3 (1.4 - 3.8) \]
\[ p = 0.001^* \]

CMS4 vs. CMS2
\[ HR = 1.5 (1.1 - 2.1) \]
\[ p = 0.008^* \]

* Adjusted for stage, MSI, BRAF mut, and stratified by dataset.
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency


Pembrolizumab efficacy according to MMR status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mismatch Repair–Deficient Colorectal Cancer (N = 11)</th>
<th>Mismatch Repair–Proficient Colorectal Cancer (N = 21)</th>
<th>Mismatch Repair–Deficient Noncolorectal Cancer (N = 9)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer type — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Colon</td>
<td>9 (82)</td>
<td>18 (86)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>2 (18)</td>
<td>3 (14)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ampullary or cholangiocarcinoma</td>
<td>0</td>
<td>NA</td>
<td>4 (44)</td>
<td></td>
</tr>
<tr>
<td>Endometrial</td>
<td>0</td>
<td>NA</td>
<td>2 (22)</td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>0</td>
<td>NA</td>
<td>2 (22)</td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>0</td>
<td>NA</td>
<td>1 (11)</td>
<td></td>
</tr>
<tr>
<td>Detected germline mutation or known Lynch syndrome — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>9 (82)</td>
<td>0</td>
<td>4 (44)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2 (18)</td>
<td>21 (100)</td>
<td>4 (44)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>1 (11)</td>
<td></td>
</tr>
<tr>
<td>BRAF wild type — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.64</td>
</tr>
<tr>
<td>Yes</td>
<td>8 (73)</td>
<td>11 (52)</td>
<td>4 (44)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>1 (5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (27)</td>
<td>9 (43)</td>
<td>5 (56)</td>
<td></td>
</tr>
<tr>
<td>KRAS wild type — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (55)</td>
<td>13 (62)</td>
<td>4 (44)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5 (45)</td>
<td>8 (38)</td>
<td>1 (11)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>4 (44)</td>
<td></td>
</tr>
</tbody>
</table>

**Pembrolizumab and MMR Status: results**

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>Mismatch Repair–Deficient Colorectal Cancer (N=10)</th>
<th>Mismatch Repair–Proficient Colorectal Cancer (N=18)</th>
<th>Mismatch Repair–Deficient Noncolorectal Cancer (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response — no. (%)</td>
<td>0</td>
<td>0</td>
<td>1 (14)*</td>
</tr>
<tr>
<td>Partial response — no. (%)</td>
<td>4 (40)</td>
<td>0</td>
<td>4 (57)†</td>
</tr>
<tr>
<td>Stable disease at week 12 — no. (%)</td>
<td>5 (50)</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Progressive disease — no. (%)</td>
<td>1 (10)</td>
<td>11 (61)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Could not be evaluated — no. (%)</td>
<td>0</td>
<td>5 (28)</td>
<td>0</td>
</tr>
<tr>
<td>Objective response rate (95% CI) — %</td>
<td>40 (12–74)</td>
<td>0 (0–19)</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>Disease control rate (95% CI) — %</td>
<td>90 (55–100)</td>
<td>11 (1–35)</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>Median duration of response — wk</td>
<td>Not reached</td>
<td>NA†</td>
<td>Not reached</td>
</tr>
<tr>
<td>Median time to response (range) — wk</td>
<td>28 (13–35)</td>
<td>NA†</td>
<td>12 (10–13)</td>
</tr>
</tbody>
</table>

Clinical Responses to Pembrolizumab Treatment.


CEA, Ca19.9, Ca125
Clinical Benefit of Pembrolizumab Treatment According to Mismatch-Repair Status.

Updated results of Pembrolizumab in MSI tumors

Table 2 Objective Responses for Subjects Enrolled in KN 016

<table>
<thead>
<tr>
<th>Type of Response-no. (%)</th>
<th>MSI-H CRC</th>
<th>MSS CRC</th>
<th>MSI-H non-CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>0(0)</td>
<td>0(0)</td>
<td>1(10)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>8(62)</td>
<td>0(0)</td>
<td>5(50)</td>
</tr>
<tr>
<td>Stable Disease (Week 12)</td>
<td>4(30)</td>
<td>4(16)</td>
<td>1(10)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>1(8)</td>
<td>14(56)</td>
<td>2(20)</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>0(0)</td>
<td>7(28)</td>
<td>1(10)</td>
</tr>
<tr>
<td>Objective response rate</td>
<td>62%</td>
<td>0%</td>
<td>60%</td>
</tr>
<tr>
<td>95% CI</td>
<td>32-86</td>
<td>0-14</td>
<td>26-88</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>92%</td>
<td>16%</td>
<td>70%</td>
</tr>
<tr>
<td>95% CI</td>
<td>64-100</td>
<td>5-36</td>
<td>35-93</td>
</tr>
</tbody>
</table>
Keynote-177

A Phase III Study of Pembrolizumab (MK-3475) vs. Chemotherapy in Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Carcinoma (KEYNOTE-177)

EudraCT NUMBER: 2015-002024-89

1st-line mCRC

Statistics:
1st EP: PFS
- HR 0.55 (1-sided)
2nd EP: OS
- HR 0.65 (1-sided)

N patients: 270
40% of screened patients were PD-L1+
### Best Overall Response, RECIST v1.1

<table>
<thead>
<tr>
<th></th>
<th>Central Review N = 36&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Investigator Review N = 39</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR&lt;sup&gt;b&lt;/sup&gt; % (95% CI)</strong></td>
<td>22.2 (10.1-39.2)</td>
<td>33.3 (19.1-50.2)</td>
</tr>
<tr>
<td><strong>Best overall response, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 (22.2)</td>
<td>13 (33.3)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5 (13.9)</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>19 (52.8)</td>
<td>23 (59.0)</td>
</tr>
<tr>
<td>No assessment&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 (2.8)</td>
<td>0</td>
</tr>
<tr>
<td>Not determined&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3 (8.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Central review N = 36

<sup>b</sup> ORR is overall response rate

<sup>c</sup> No assessment

<sup>d</sup> Not determined

Bang Y ASCO 2015 Abst 4001
Keynote-012 Gastric cohort anti PDL-1 Pembrolizumab

Bang Y ASCO 2015 Abst 4001
GC Subtypes have different Molecular and Pathological features

Chromosomal Instability (CIN) (50%)
- Intestinal-type GCs
- TP53 mutations
- Focal somatic gene amplifications in RTK/RAS genes

Genome Stable (GS) (20%)
- Diffuse-type GC
- Less mutation
- CDH1, RHOA** mutations

Microsatellite Instability (MSI) (20%)
- Intestinal-type GC
- TGFBR2, ACVR2A mutations

Epstein-Barr Virus (EBV) (10%)
- Global hypermethylation
- PDL-1/2 Gene Amplification**

Better prognosis
Pembrolizumab (MK-3475) For PD-L1–Positive Squamous Cell Carcinoma of the Anal Canal: Preliminary Safety and Efficacy Results From KEYNOTE-028

Patrick A. Ott, 1 Sarina A. Piha-Paul, 2 Pamela Munster, 3 Michael J. Pishvajian, 4 Emilie van Brummelen, 5 Roger B. Cohen, 6 Carlos Gomez-Roca, 7 Samuel Ejadi, 8 Mark Stein, 9 Emily Chan, 10 Matteo Simonelli, 11 Anne Morosky, 12 Sanatan Saraf, 12 Minori Koshiji, 12 Jaafar Bennouna 13

1 Dana-Farber Cancer Institute, Boston, USA; 2 University of Texas MD Anderson Cancer Center, Houston, USA; 3 UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, USA; 4 Georgetown University, Washington DC, USA; 5 Netherlands Cancer Institute, Amsterdam, Netherlands; 6 University of Pennsylvania, Philadelphia, PA, USA; 7 Institut Claudius Regaud, Toulouse, France; 8 Virginia G. Piper Cancer Center, Scottsdale, AZ, USA; 9 Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; 10 Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; 11 Humanitas Cancer Center, Rozzano, Italy; 12 Merck & Co., Inc., Kenilworth, NJ, USA; 13 Institut de Cancérologie de l'Ouest, Nantes, France
PD-L1 Screening: Anal Cancer Cohort

Patients With Tumor Samples Evaluable for PD-L1
n = 43

PD-L1–Positive Tumors
n = 32

74.4% PD-L1+

Patients Enrolled
N = 25

Reasons for exclusion
• Inadequate organ function (n = 1)
• No measurable disease (n = 1)
• Pregnancy (n = 1)
• Other eligibility criteria not met (n = 1)
• Cohort fully enrolled (n = 3)

Data cutoff date: July 1, 2015.
# Anal Canal Cancer: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>N = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>63 (46–82)</td>
</tr>
<tr>
<td>Female</td>
<td>23 (92)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>19 (76)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Not specified</td>
<td>5 (20)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5 (20)</td>
</tr>
<tr>
<td>1</td>
<td>20 (80)</td>
</tr>
<tr>
<td>Histology at baseline, n (%)</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>22 (88)</td>
</tr>
<tr>
<td>Carcinoid(^a)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Endometrioid(^a)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Mucoepidermoid(^a)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>N = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant or neoadjuvant systemic therapy, n (%)</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Prior lines of therapy for advanced disease, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3 (12)</td>
</tr>
<tr>
<td>1</td>
<td>7 (28)</td>
</tr>
<tr>
<td>2</td>
<td>7 (28)</td>
</tr>
<tr>
<td>≥3</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Prior therapies for advanced disease(^b)</td>
<td></td>
</tr>
<tr>
<td>5-FU + mitomycin</td>
<td>15 (60)</td>
</tr>
<tr>
<td>5-FU ± platinum ± other</td>
<td>14 (56)</td>
</tr>
<tr>
<td>Gemcitabine + platinum ± other</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Chk-1 inhibitor</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Etitinotecan pegol</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (20)</td>
</tr>
</tbody>
</table>

\(^a\) Protocol violations.

\(^b\) Patients could have received >1 prior therapy.

Data cutoff date: July 1, 2015.
### Anal Canal Cancer: Antitumor Activity
(RECIST v1.1, Investigator Review)

<table>
<thead>
<tr>
<th>Best Response</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0.0–13.7</td>
</tr>
<tr>
<td>Partial response&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5</td>
<td>20</td>
<td>6.8–40.7</td>
</tr>
<tr>
<td>Stable disease</td>
<td>11</td>
<td>44</td>
<td>24.4–65.1</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>8</td>
<td>32</td>
<td>14.9–53.5</td>
</tr>
<tr>
<td>Not assessed&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1</td>
<td>4</td>
<td>0.1–20.4</td>
</tr>
</tbody>
</table>

- ORR: 20.0% (95% CI, 6.8–40.7)
- DCR: 64.0% (95% CI, 42.5–82.0)

<sup>a</sup>Includes unconfirmed responses (n = 1).
<sup>b</sup>Patient discontinued therapy due to toxicity prior to the first postbaseline response evaluation.

Data cutoff date: July 1, 2015.
Anal Canal Cancer: Maximum Change From Baseline in Tumor Size

Includes patients with ≥1 postbaseline tumor assessment (n = 24).
Data cutoff date: July 1, 2015.
Anal Canal Cancer Longitudinal Change From Baseline in Tumor Size

Includes patients with \(\geq 1\) postbaseline tumor assessment (n = 24).
Data cutoff date: July 1, 2015.
Anal Canal Cancer: Treatment Exposure and Response Duration

- Median time to response: 15.6 wk (range, 7.1–21.0)
- Median response duration: Not reached (range, <0.1+ to 9.2+ mo)
- 3 of 5 responses ongoing at time of analysis
- Median stable disease duration: 3.6 mo (range, 1.8+ to 11.0+)

Includes patients with ≥1 postbaseline tumor assessment (n = 24).
The length of each bar represents the time to the last radiography assessment.
Data cutoff date: July 1, 2015.
Anal Canal Cancer Conclusions

- Promising, durable antitumor activity in a heavily pretreated population of PD-L1–positive squamous cell anal carcinoma
- Manageable safety profile consistent with previous experience for pembrolizumab in advanced cancer
- Data support future evaluation of pembrolizumab for advanced anal carcinoma
Immunotherapy of GI Cancer conclusion

- As in other tumor types, immunotherapy is extensively explored in GI tumors
- So far most agents are still in early phase evaluation
- Immune check point inhibitors have shown efficacy in MSI+ mCRC, Biliary tract cancer, oesogastric carcinomas and anal canal cancer
- No drug at the present time is approved and can be recommended in the ESMO Guidelines.
Monoclonal Antibodies

A phase II trial of RO5520985, a bispecific anti-ANG-2/anti-VEGF-A antibody, in patients with untreated metastatic colorectal cancer (NCT02141295).

A phase II trial of Sym004, an antibody targeting the cancer antigen EGFR (epidermal growth factor receptor), in patients with metastatic colorectal cancer (NCT02083653).

A phase I/II trial testing IMMU-132, an antibody-drug conjugate targeting Trop-2, in patients with epithelial cancers (NCT01631552).

A phase I/II trial of IMMU-130, an antibody-drug conjugate targeting CEACAM5, which is expressed on the surface of a majority of solid tumors, in patients with metastatic colorectal cancer (NCT01605318).

A phase I/II trial of ensituximab (NPC-1C), an antibody against a MUC5AC-related antigen, in patients with recurrent, locally advanced colorectal cancer after standard therapy (NCT01040000).

A phase I trial of bavituximab, an antibody that targets an immune-suppressing molecule in tumors, in patients with rectal cancer (NCT01634685).

A phase I trial of MORAb-066, targeting tissue factor (TF), an antigen overexpressed in tumor cells and tumor endothelial cells, in patients with TF-expressing cancers, including colorectal cancer (NCT01761240).

A phase I trial of the anti-MIF antibody, which targets macrophage migration inhibitory factor, in patients with colorectal cancer (NCT01765790).

A phase I study of MGD007, a dual-affinity re-targeting (DART) protein designed to target the glycoprotein A33 antigen, which is found on 95% of colorectal cancers, in patients with metastatic colorectal cancer (NCT02248805).
Immunotherapy of Colorectal cancer

Checkpoint Inhibitors and Immune Modulators

A phase II study of pembrolizumab (Keytruda®, MK-3475), a PD-1 antibody made by Merck, for patients with microsatellite unstable (MSI) tumors, including colorectal cancer (NCT01876511).

A phase I/II trial of MEDI4736, an anti-PD-L1 checkpoint inhibitor made by MedImmune/AstraZeneca, in patients with solid tumors (NCT01693562).

A phase I/II trial of MEDI6469, an anti-OX40 agonist antibody, alone or with tremelimumab, an anti-CTLA-4 antibody, and/or MEDI4736 (NCT02205333).

A phase I/II trial of nivolumab (Opdivo®), an anti-PD-1 antibody, +/- ipilimumab (Yervoy®), an anti-CTLA-4 antibody, in patients with recurrent and metastatic colon cancer (NCT02060188).

A phase I/II trial of ipilimumab in patients with advanced solid tumors which have spread to the liver, lung, or adrenal gland (NCT02239900).

A phase I trial of tremelimumab (anti-CTLA-4) and MEDI4736 (anti-PD-L1) in patients with advanced solid tumors, including colorectal cancer (NCT01975831). This trial is sponsored by Ludwig Cancer Research in partnership with the Cancer Research Institute. Another phase I trial of tremelimumab and MEDI4736 is for patients with solid tumors (NCT02261220).

A phase I trial of MEDI6383, an anti-OX40 antibody, for patients with advanced solid tumors (NCT02221960).

A phase I trial of MEDI0680 (AMP-514), an anti-PD-1 antibody, and MEDI4736 in patients with advanced cancers (NCT02118337).

Two phase I trials to test MPDL3280A, an anti-PD-L1 antibody being developed by Roche/Genentech, in patients with several cancers (NCT01375842, NCT01633970).

A phase I study of MSB0010718C, an anti-PD-L1 antibody being developed by EMD Serono, in solid tumors (NCT01772004).

A phase I trial with urelumab, an anti-4-1BB/CD137 antibody developed by Bristol-Myers Squibb, in patients with colorectal cancer (NCT02110082).

A phase I trial testing urelumab, an anti-4-1BB/CD137 antibody, in patients with advanced cancers (NCT02013804).

A phase I trial to test varilimumab (CDX-1127), an anti-CD27 antibody made by Celldex, in patients with several cancers, including colorectal cancer (NCT01460134).

A phase I trial to test varilimumab (CDX-1127) and nivolumab (Opdivo®) in patients with advanced solid tumors, including colorectal cancer (NCT02335918).

A phase I trial of MOXR0916, an anti-OX40 antibody being developed by Roche/Genentech, in patients with advanced cancer (NCT02219724).

A phase I trial to test BMS-986016, a LAG-3 antibody, with or without nivolumab (anti-PD-1), in patients with solid tumors (NCT01968109).

A phase I study of liilimumab, an anti-KIR antibody being developed by Bristol-Myers Squibb, in combination with nivolumab (anti-PD-1) in patients with advanced solid tumors (NCT01714739).

A phase I trial of TRX518, an anti-GITR antibody, in patients with advanced cancer (NCT01239134). This trial is sponsored jointly by the CRI/Ludwig Clinical Trials Network.

A phase I trial of MK-4166, an anti-GITR antibody, in patients with advanced cancer (NCT02132754).

See more at: http://www.cancerresearch.org/cancer-immunotherapy/impacting-all-cancers/colorectal-cancer#sthash.n432ZqwW.dpuf
Immunotherapy of Colorectal cancer

Cancer Vaccines
A phase III study of Imprime PGG® in combination with cetuximab in subjects with recurrent or progressive KRAS wild type colorectal cancer (PRIMUS) (NCT01309126).
A phase II trial of a vaccine that targets the NY-ESO-1 protein in patients with advanced cancer whose cancers express NY-ESO-1 (NCT01697527).
A phase I/II trial of DCVax, being developed by Northwest Biotherapeutics, in patients with solid tumors (NCT01882946).
A phase I trial of FANG in patients with advanced cancer (NCT01061840).
A phase I trial to test AVX701, which targets the CEA antigen that has been found to be associated with colorectal cancers, in patients with stage 3 colorectal cancer (NCT01890213).
A phase I study to test a vaccine targeting brachyury, which helps drive cancer metastasis, in patients with advanced cancer, including colorectal cancer (NCT02179515).
A phase I study of vaccine therapy with or without sirolimus in treating patients with NY-ESO-1 expressing solid tumors (NCT01522820).
A phase I trial of a vaccine that targets the HER2 antigen in patients with metastatic cancer, including colorectal cancer (NCT01376505).
A phase I study of a HER2 vaccine in patients with HER2-expressing tumors (NCT01730118).
- See more at: http://www.cancerresearch.org/cancer-immunotherapy/impacting-all-cancers/colorectal-cancer#sthash.n432ZqwW.dpuf
Adoptive Cell Therapy

A phase II trial using tumor-infiltrating lymphocytes (TILs) in metastatic digestive tract cancers (NCT01174121).

A phase I/II trial of T cells engineered to target VEGFR in patients with metastatic cancer (NCT01218867). A phase I/II trial of T cells engineered to target MAGE-A3 in patients with metastatic cancer that expresses MAGE-A3, including colorectal cancer (NCT02111850).

A phase I trial of T cells targeting EGFR in patients with advanced cancer, including colorectal cancer (NCT01081808).

A phase I trial to test natural killer (NK) cells, important innate immune cells, in patients with advanced cancer, including colorectal cancer (NCT00720785).
Immunotherapy of Colorectal cancer

**Oncolytic Virus Therapies**

A phase II trial to test Reolysin, a virus that is able to replicate specifically in cancer cells bearing an activated RAS pathway, in patients with metastatic colorectal cancer (NCT01622543).

**Adjuvant**

A phase I/II trial of tumor necrosis factor and rintatolimod, which binds to Toll-like receptor 3 (TLR3), in patients with recurrent resectable colorectal cancer (NCT01545141).

**Cytokines**

A phase I trial of AM0010, a recombinant human interleukin 10 (IL-10), in patients with advanced solid tumors (NCT02009449).


- See more at: http://www.cancerresearch.org/cancer-immunotherapy/impacting-all-cancers/colorectal-cancer#sthash.n432ZqwW.dpuf