New kids on the block: Immunotherapy in melanoma and GI Malignancies

Ralph P.W. Wong, MD FRCPC
"Cry 'Havoc!', and let slip the dogs of war"

*Julius Caesar Act iii. Sc. 1*

UPCON Primary Care Conference
Ralph P.W. Wong MD FRCPC
Disclosures

• Faculty / Speaker’s name: Ralph Wong

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  – Speakers Bureau/Honoraria: None
  – Consulting Fees: None
  – Other: None
Mitigating Potential Bias

• Not Applicable
Objectives

At the end of the presentation the learner will be able to:

1. To review the basic principles of how the immune system interacts with malignancy
2. To understand the concept of Checkpoint inhibition and its use in the management of GI malignancies and Melanoma
This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumours are paying off – even if the future remains a question mark.

Couzin-Frankel J. Science 2013;342:1432-33
Immuno-Oncology
The Immune System is Comprised of Two “Arms”: Innate and Adaptive

**Innate Immunity**
- Immediate
- First line of immune defense
- Not antigen-specific response

**Adaptive Immunity**
- Slow response
- Antigen-specific response
- Memory

- External threats: viruses, parasites, protozoa, fungi, bacteria, toxins
- Internal threats: cancer

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Tumour-associated antigens can trigger a tumour-specific immune cell response:

- Tumours express a multitude of proteins, known as tumour-associated antigens$^{1,2,3,4}$
- Antigen presenting cell (APC) captures tumour-associated antigens$^2$
- Activated APC can interact with T cells$^4$
T-cell Activation: Cytotoxic T cells

Activated APC presents the tumour-associated antigen to the T cell along with a co-stimulatory signal\(^1\)

Inactive T cell

Active, cytotoxic (killer) T cells

Antigen recognition

Antigen

Co-stimulatory signal

Activated T cell

T cells proliferate

Cytotoxic T cell induces apoptosis in tumour cell\(^1\)

The Cancer – Immunity Cycle

Mechanisms for Cancer to Evade the Immune System
• Normal conditions:
  – There are a number of immune activation and inhibition pathways that modulate the immune response and protect healthy tissues from collateral damage\(^1,7\)

• Tumour evasion of the immune system may be associated with an imbalance in immune activation and inhibition.\(^1-5\)

Tumours may down-regulate co-stimulatory pathways.\(^2,3\)
Co-stimulatory receptors include:
• CD28
• CD40
• OX40
• CD137
• GITR

Tumours may up-regulate immune checkpoints (inhibitory signaling pathways).\(^2,3,5,6\)
Checkpoint pathway molecules include:
• LAG-3
• CTLA-4
• B7-H3
• PD-1
• TIM-3

T-cell Checkpoint Regulation

• T-cell responses are regulated through a complex balance of inhibitory ("checkpoint") and activating signals

• Tumours can dysregulate these pathways and consequently, the immune response

• Targeting these pathways is an evolving approach to cancer therapy

Mechanisms for Cancer to Evade the Immune System
Many tumours escape the immune response by creating an immunosuppressive microenvironment that prevents an effective antitumour response.\textsuperscript{1,2}

The mechanisms tumours use to escape the immune system provide a range of potential therapeutic targets for cancer.

Checkpoint inhibition as a way to awaken the immune system
Multiple Potential I-O Targets to Activate the Immune System

- Antitumour response is a net balance of complex inhibitory and stimulatory interactions between APC, T cell, and tumour

- Multiple potential I-O targets, such as:
  - T-cell co-stimulatory receptors
  - T-cell checkpoint/inhibitory receptors
  - APC
  - Microenvironment

- Modulation of these targets by I-O therapies may activate the immune system to eliminate the tumour

Immuno-oncology: Blocking CTLA-4 and PD-1 Pathways with Monoclonal Antibodies

CTLA-4 pathway blockade

PD-1 pathway blockade

CTLA-4=cytotoxic T-lymphocyte antigen-4; PD-1=programmed cell death 1; PD-L1/2=PD ligand 1/2; TCR=T cell receptor.

CLTA-4 Monoclonal Antibodies
Tumor-specific Antigenic Peptides Can Lead to Anti-Cancer Immune Responses

Attenuated or Terminated Proliferation

Unrestrained Proliferation

Tumor

APC

CTLA-4

CTLA-4: Mechanism of Action (MoA)

Unrestrained Proliferation

IL-2

ipilimumab

Anti-PD-1/L1
PD-1 and PD-L1 Antibodies

- PD-1 – inhibitory receptor found on activated lymphocytes and monocytes and is associated with tumour immune escape
- Binds with PD-L1 on tumour cells
- Interaction between PD-1 and PD-L1 suppresses the cytotoxic T-cell response

Adapted from *N Engl Med.* 2012;366(26):2517
Potential Clinical Response Patterns with I-O Therapeutic Approaches
Response to I-O Therapy is a Multi-step Process that May Impact Response Kinetics

Therapies that affect the immune system may not induce a measurable impact on tumour growth immediately after administration\(^1\)

<table>
<thead>
<tr>
<th>I-O Start(^2)</th>
<th>Immune cell activation and proliferation</th>
<th>Effect on tumour</th>
<th>Effect on survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Initial I-O therapy administration</td>
<td>Several Weeks</td>
<td>Several Months</td>
</tr>
<tr>
<td></td>
<td>Initial I-O therapy administration</td>
<td>Several Weeks</td>
<td>Several Weeks</td>
</tr>
<tr>
<td></td>
<td>Immune cell activation and proliferation start early on after initial I-O administration</td>
<td>Clinically measurable immune-mediated antitumour effects occur over weeks to months</td>
<td>Potential effect on survival may occur several months after initial I-O administration</td>
</tr>
</tbody>
</table>

Potential Tumour Response Patterns to Therapy

Response in baseline lesions typically seen with chemotherapy, but also I-O therapies and targeted therapies. Captured by existing RECIST and WHO criteria

“Stable disease”: Slow, steady decline in tumour volume seen with chemotherapy, targeted and I-O therapies. Captured by existing RECIST and WHO criteria

Therapy start

- Thresholds for response or progressive disease (RECIST)

Graphs for illustrative purposes showing responses to ipilimumab in advanced melanoma

Potential Tumour Response Patterns to Therapy

Response after initial increase in tumour volume; novel and specific to I-O therapy. RECIST or WHO criteria may not be appropriate to assess.

Reduction in tumour burden after appearance of new lesions; novel and specific to I-O therapy. RECIST or WHO criteria may not be appropriate to assess.

Some vaccines may not follow similar patterns of response as other I-O therapies.

Example of Evolution of Response to CTLA-4 Inhibition

Week 96: Durable and ongoing response without signs of irAEs

Week 12:
Initial increase in total tumour burden (mWHO PD)

Week 16:
Responding

Week 12:
Initial increase in total tumour burden (mWHO PD)

Week 16:
Responding

irAE = immune-related adverse events

Harmankaya K, et al. Presented at the World Meeting of Interdisciplinary Melanoma/Skin Cancer Centers: November 19 - 21, 2009; Berlin, Germany.
Pseudo-progression: Inflammation Causes Swelling, May Appear as Tumour Growth or New Lesions Upon Imaging\(^1\)

Considerations when evaluating true progression vs. pseudo-progression

<table>
<thead>
<tr>
<th></th>
<th>May indicate progression</th>
<th>May indicate pseudo-progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Performance status</strong></td>
<td>Deterioration of performance</td>
<td>Remains stable or improves</td>
</tr>
<tr>
<td><strong>Systemic symptoms</strong></td>
<td>Worsen</td>
<td>May or may not improve</td>
</tr>
<tr>
<td><strong>Symptoms of tumour enlargement</strong></td>
<td>Present</td>
<td>May or may not be present</td>
</tr>
<tr>
<td><strong>Tumour burden</strong></td>
<td>Increase</td>
<td>Increase followed by response</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>Appear and increase in size</td>
<td>Appear then remain stable and/or subsequently respond</td>
</tr>
<tr>
<td><strong>New lesions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Biopsy may reveal</strong></td>
<td>Evidence of tumour growth</td>
<td>Evidence of T-cell infiltration</td>
</tr>
</tbody>
</table>

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Clinical Efficacy of Immuno-oncology Treatment
Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs.

Mutational heterogeneity in cancer-altered proteins contain neoepitopes for immune recognition.

Melanoma
Chemotherapy
(1976-2014)
Landmark Meta-analysis: Overall Survival (OS) in Metastatic Stage IV Melanoma

Median OS: 6.2 months

- 25.5% alive at 1 year
- Only ~10% alive at 24 months

Survival data from 42 phase II trials with over 2100 stage IV patients

Ipilimumab: Pooled Survival Analysis from Phase II/III Trials in Advanced Melanoma

N = 1861
Median OS (95% CI): 11.4 mo (10.7-12.1)
3-year OS Rate (95% CI): 22% (20% to 24%)

Patients at Risk
Ipilimumab 1861 839 370 254 192 170 120 26 15 5 0

• Historical controls
  – Phase II: 1278 patients in 42 cooperative group trials from 1975 to 2005
  – Phase III: 3739 patients in 10 trials from 1999 to 2011
CHECKMATE 066 and KEYNOTE 006: Overall survival

Nivolumab vs DTIC in \textit{BRAF}-negative, previously untreated melanoma$^{[1]}$

- HR for death: 0.42 (99.79\% CI: 0.25-0.73; $P < .001$)
- mOS (95\% CI): Not reached
- Nivolumab
- Dacarbazine

- Nivolumab
- Dacarbazine
- mOS (95\% CI): Not reached
- 10.8 mos (9.3-12.1)

Pembrolizumab vs Ipilimumab in Advanced Melanoma$^{[2]}$

- Pembrolizumab q3w
- Pembrolizumab q2w
- Ipilimumab

CTLA 4/PD-1 combination
Case Presentation

- 56 yr. old female 4.9 mm ulcerated (T4b, Nx M0) BRAF wild type, NRAS mutated melanoma right upper arm resected April 2016

- declined adjuvant interferon
Case Presentation

• October 2016, presents to clinic with increasingly severe axillary pain, hoarse voice
• Exam confirmed large mass in right axilla, right arm swelling and inability to abduct arm
• Pain syndrome consistent with brachial plexopathy
Case Presentation

October 30, 2016
Case Presentation

- Offered clinical trial with nivolumab/ipilimumab
- Commenced therapy November 24, 2016
- Noted decreased mass and pain after one cycle, hoarse voice resolved
- Developed Grade 1 rash after third cycle Jan 6, 2017
CHECKMATE 067: Phase III Trial of Nivolumab + Ipilimumab vs. Nivolumab vs. Ipilimumab for First-line Treatment of Melanoma

- **Stratified by PD-L1 expression (< 5% vs ≥ 5%), BRAF status, and AJCC M stage**

  Previously untreated pts with unresectable stage III/IV melanoma and ECOG PS 0-1 (N = 945)

  - Nivo 1 mg/kg + Ipi 3 mg/kg q3w for 4 doses, then Nivo 3 mg/kg q2w (n = 314)
  - Nivo 3 mg/kg q2w + Placebo (n = 316)
  - Ipi 3 mg/kg q3w for 4 doses + Placebo (n = 315)

  Until disease progression or unacceptable toxicity

- **Coprimary endpoints:** PFS, OS
- **Secondary endpoints:** ORR, tumor PD-L1 expression and efficacy, safety

## Treatment-Related AEs Associated With Nivolumab/Ipilimumab combination

<table>
<thead>
<tr>
<th>Select Treatment-Related AEs, %</th>
<th>Nivo + Ipi (n = 313)</th>
<th>Nivo (n = 313)</th>
<th>Ipi (n = 311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Any reported AE</td>
<td>96</td>
<td>55</td>
<td>82</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>36</td>
<td>29</td>
<td>8</td>
</tr>
<tr>
<td>Skin</td>
<td>59</td>
<td>6</td>
<td>42</td>
</tr>
<tr>
<td>Pruritus</td>
<td>33</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>Rash</td>
<td>28</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>12</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>46</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>44</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Colitis</td>
<td>12</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic</td>
<td>30</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>ALT increase</td>
<td>18</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>AST increase</td>
<td>15</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Endocrine</td>
<td>30</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15</td>
<td>&lt; 1</td>
<td>9</td>
</tr>
</tbody>
</table>
## Updated Response To Treatment

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>58.9 (53.3–64.4)</td>
<td>44.6 (39.1–50.3)</td>
<td>19.0 (14.9–23.8)</td>
</tr>
<tr>
<td><strong>Best overall response — %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>17.2</td>
<td>14.9</td>
<td>4.4</td>
</tr>
<tr>
<td>Partial response</td>
<td>41.7</td>
<td>29.7</td>
<td>14.6</td>
</tr>
<tr>
<td>Stable disease</td>
<td>11.5</td>
<td>9.8</td>
<td>21.3</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>23.6</td>
<td>38.6</td>
<td>51.1</td>
</tr>
<tr>
<td>Unknown</td>
<td>6.1</td>
<td>7.0</td>
<td>8.6</td>
</tr>
<tr>
<td><strong>Median duration of response, months (95% CI)</strong></td>
<td>NR (NR–NR)</td>
<td>31.1 (31.1–NR)</td>
<td>18.2 (8.3–NR)</td>
</tr>
</tbody>
</table>

*By RECIST v1.1; NR = not reached.

- At the 18-month DBL, the CR rate for NIVO+IPI, NIVO and IPI was 12.1%, 9.8% and 2.2%, respectively

Database lock: Sept 13, 2016, minimum f/u of 28 months
Updated Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>Nivo + Ipi (n = 314)</th>
<th>Nivo (n = 316)</th>
<th>Ipi (n = 315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos (95% CI)</td>
<td>11.7 (8.9-21.9)</td>
<td>6.9 (4.3-9.5)</td>
<td>2.9 (2.8-3.2)</td>
</tr>
<tr>
<td>HR (99.5% CI) vs Ipi</td>
<td>0.42 (0.34-0.51)*</td>
<td>0.54 (0.43-0.66)*</td>
<td>–</td>
</tr>
<tr>
<td>HR (95% CI) vs Nivo</td>
<td>0.76 (0.60-0.94)†</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Patients at risk:

<table>
<thead>
<tr>
<th>Patients at risk:</th>
<th>NIVO+IPI</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>314</td>
<td>218</td>
<td>176</td>
<td>156</td>
</tr>
<tr>
<td>316</td>
<td>178</td>
<td>151</td>
<td>132</td>
</tr>
<tr>
<td>315</td>
<td>136</td>
<td>77</td>
<td>58</td>
</tr>
</tbody>
</table>

Database lock: Sept 13, 2016, minimum f/u of 28 months

AACR Presentation April 3, 2017
### Overall Survival

**Median OS, mo (95% CI)**
- **NIVO+IPI (N=314)**: NR
- **NIVO (N=316)**: NR (29.1–NR)
- **IPI (N=315)**: 20.0 (17.1–24.6)

**HR (98% CI) vs. IPI**
- **NIVO+IPI (N=314)**: 0.55 (0.42–0.72)*
- **NIVO (N=316)**: 0.63 (0.48–0.81)*
- **IPI (N=315)**: --

**HR (95% CI) vs. NIVO**
- **NIVO+IPI (N=314)**: 0.88 (0.69–1.12)
- **NIVO (N=316)**: --
- **IPI (N=315)**: --

*P<0.0001

**Patients at risk:**
- **NIVO+IPI**: 314, 292, 265, 247, 226, 221, 209, 200, 198, 192, 170, 49, 7, 0
- **NIVO**: 316, 292, 265, 244, 230, 213, 201, 191, 181, 175, 157, 55, 3, 0
- **IPI**: 315, 285, 254, 228, 205, 182, 164, 149, 136, 129, 104, 34, 4, 0

Database lock: Sept 13, 2016, minimum f/u of 28 months

AACR April 6, 2017
GI Malignancies
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

## PD-1 Blockade in MMR-Deficient Tumors: Patient Population

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>MMR-Deficient CRC (n = 13)</th>
<th>MMR-Proficient CRC (n = 25)</th>
<th>MMR-Deficient Other Tumors (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs</td>
<td>46</td>
<td>62</td>
<td>59</td>
</tr>
<tr>
<td>Diagnosis, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ CRC</td>
<td>100</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>▪ Ampullary/biliary</td>
<td>0</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>▪ Endometrial</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>▪ Small bowel</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>▪ Prostate</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>▪ Gastric</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>≥ 2 prior therapies, %</td>
<td>100</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>Lynch syndrome, %</td>
<td>85</td>
<td>0</td>
<td>40</td>
</tr>
</tbody>
</table>

PD-1 Blockade in MMR-Deficient Tumors: Efficacy

<table>
<thead>
<tr>
<th>Efficacy Outcome (RECIST), %</th>
<th>MMR-Deficient CRC (n = 13)</th>
<th>MMR-Proficient CRC (n = 25)</th>
<th>MMR-Deficient Other tumors (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>62</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>92</td>
<td>16</td>
<td>70</td>
</tr>
</tbody>
</table>

- To date, responses > 1 yr. observed, and 13 or 14 responding pts continue to maintain response
- Other efficacy outcomes in MMR-deficient vs MMR-proficient tumors
  - Median PFS: not yet reached vs 2.3 mos
  - Median OS: not yet reached vs 5 mos
- Biochemical response (eg, CEA, CA-19) declined early with treatment in pts with MMR-deficient cancers and correlated with ORR, PFS, OS

Clinical Responses to Pembrolizumab Treatment.

Anal cancer
Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study

• Phase III trials are underway in gastric cancer and hepatoma where PD-1 inhibition has shown activity

• Stay tuned......
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Nivolumab/Ipilimumab</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
<th>Atezolizumab</th>
<th>Avelumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC 1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td></td>
<td></td>
<td></td>
<td>Oct 2016 PD-L1 +ve</td>
<td></td>
</tr>
<tr>
<td>Renal Cancer 2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>Nov 2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkins’ (Refractory)</td>
<td></td>
<td></td>
<td></td>
<td>May 2016</td>
<td></td>
</tr>
<tr>
<td>SCCHN 2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>Nov 2016</td>
<td></td>
<td>Aug 2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder Ca 2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>Feb 2017</td>
<td></td>
<td></td>
<td>May 2016</td>
<td></td>
</tr>
<tr>
<td>Merkel Cell &gt;1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td></td>
<td></td>
<td></td>
<td>March 2017</td>
<td></td>
</tr>
</tbody>
</table>
Health Canada Approvals

- **Melanoma (1\textsuperscript{st} and 2\textsuperscript{nd} line)**
  - Nivolumab/ipilimumab
  - Nivolumab
  - Pembrolizumab

- **Lung Cancer (2\textsuperscript{nd} line)**
  - Nivolumab
  - Pembrolizumab (PD-L1 +ve)

- **Renal Cancer (2\textsuperscript{nd} line)**
  - Nivolumab
Unanswered questions
Quo Vadis?
Combining anticancer agents with Immunotherapy

Radiotherapy  
Antitumor agents  
Oxaliplatin  

Cyclophosphamide  
5-Fluorouracil  
Gemcitabine  

Dendritic cell  
Induction of immunogenic tumor cell death  

CTLA4  
PD-L1  

CD8 T cell  

Regulatory T cell  
Myeloid derived suppressor cell  
Elimination of immunosuppressive cells

Fas  
Tumor bed  

Anti-CTLA4  
Anti-PD-1  

Checkpoint inhibitor blockade  

IL-2  
IL-15  
IL-21  
Cytokines  

Radiotherapy  
5-Fluorouracil  
Dacarbazine  
Sensitization to T cell lysis

The landscape of T cell activating and inhibitory receptors
Turning a “cold” tumour “hot”; Colon cancer

- Open-label phase Ib dose escalation and expansion study

3 + 3 Dose Escalation

Pts with chemo-refractory solid tumors, ECOG PS 0-1, measurable disease per RECIST v1.1

Cobimetinib* 20,† 40, or 60‡ mg PO QD +
Atezolizumab 800 mg IV Q2W

Dosed in cycles of 21 days on/7 days off.

†1 KRAS mutant pt, 1 KRAS WT pt.
‡1 KRAS mutant pt.

- Dose-escalation: 3 mCRC pts (2 KRAS mutant, 1 KRAS WT); 28-day DLT window for MTD determination
- Dose-expansion: 20 mCRC pts (all KRAS mutant); other cohorts included NSCLC, metastatic melanoma, solid tumors serial biopsy
- Primary objectives: safety, clinical activity

• Response/tumor volume reduction not associated with PD-L1 status
• 4 pts had PRs, 3 of which were mismatch repair proficient (1 not evaluable)
• Median time to first response: 3.7 mos (range: 1.8 to 4.1)
• Median DOR: NR (range: 5.4 to 11.1 mos)
  – 2 pts with ongoing responses
• Increased intratumoral CD8 T-cell infiltration over BL in the mCRC cohort

### Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>KRAS-Mutant CRC (n = 20)</th>
<th>All CRC (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>PR</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>SD</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>PD</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>NE</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

**PFS**
- Median, mos (95% CI): 2.3 (1.8-9.5) (KRAS-Mutant CRC) vs 2.3 (1.8-9.5) (All CRC)
- 6-mo, % (95% CI): 39 (0.16-0.61) (KRAS-Mutant CRC) vs 35 (0.14-0.56) (All CRC)

**OS**
- Median, mos (95% CI): NE (6.5-NE) (KRAS-Mutant CRC) vs NE (6.5-NE) (All CRC)
- 6-mo, % (95% CI): 77 (0.57-0.97) (KRAS-Mutant CRC) vs 72 (0.52-0.93) (All CRC)

Issues
Case Presentation

Oct 22, 2015  December 30, 2015
Case Presentation

May 26, 2016

February 8, 2017
I/O therapy

The NEW “Tsunami”
Conclusion

• This is an exciting time to be in Medical Oncology
• The new I-O drugs are changing the way we look at managing patient with advanced cancer
• Previously untreated Stage IV melanoma patients are now experiencing long term survival
Conclusion

• Checkpoint inhibitors have yet to have a defined role in GI malignancies but would expect that to change in the near future especially for SCC anus
  – Phase III trial underway in gastric cancer and hepatoma
We have only scratched the surface of what the immune system can potentially be harnessed to do in treating cancer patients.
"This is one of those new miracle drugs. If you can afford it, it’s a miracle."