Immune checkpoint Blockade

NCI CCR TRACO
Stephanie L. Goff, MD
Objectives

• The basics of immunotherapy
• Mechanism of action of checkpoint blockade
• Early clinical experience and the discovery of immune related adverse events
• Checkpoint blockade in melanoma
  – Ipilimumab
  – Nivolumab
  – Pembrolizumab
• Experimental Questions
Oncology

Chemotherapy
Radiation
Surgery
Immunotherapy
Cancer Immunotherapy

1. Nonspecific stimulation of immune reactions
   a) Stimulate effector cells
   b) Inhibit regulatory factors (checkpoint blockade)

2. Active immunization to enhance anti-tumor reactions (cancer vaccines)

3. Passively transfer activated immune cells with anti-tumor activity (adoptive immunotherapy)
Immune system

Cells of the Immune System

- Checkpoint blockade primarily affects T cells
T cell birth

- Builds a repertoire of T cells
- Signal 1: Specificity
- TCR engages antigen in context of MHC
T cell activation

- Signal 2: Activation vs. Anergy

Chen 2013
Nature Reviews Immunology
• Signal 3: Polarization
• Dependent on cytokine profile of the microenvironment
The role of Signal 2 checkpoints

• Immune checkpoints promote self-tolerance
  – Initial response to antigen occurs primarily in secondary lymphoid organs (lymph nodes, tonsils, spleen, Peyer’s patches, mucosa associated lymphoid tissue)

• Immune checkpoints limit “collateral damage”
  – Effector recognition in peripheral tissue/tumor

• For cancer immunotherapy, two opportunities to break tolerance to self-antigen
Naïve and memory T cells express surface CD28
- CTLA-4 is transported to the surface in correlation to the strength of CD28 stimulation
- CTLA-4 also competes with higher affinity for CD80/86
- A dampening effect on downstream processing
- Constitutively present on Treg cells
• A primed T-cell is heading to peripheral tissue to engage a target, and once activated begin to express PD-1
• Inflammation present in the tissue can promote upregulation of the ligands of PD-1
• In general, this limits collateral damage during cell-mediated destruction of infection
PD-1/PD-L1

PD-1/PD-L1 in cancer

- Cancer cells can increase the amount of PDL1
- Successful T-cell tumor destruction can increase PDL1 through upregulation in response to IFNγ
Checkpoint blockade

Checkpoint Blockade

- Where to start?
- Tumors known to respond to other immunotherapy

- Melanoma
  - Estimated 9,940 deaths/year in US
  - Metastatic disease 16% 5 yr survival
  - Interleukin-2 durable cure in 4%

- Renal Cell Cancer
  - Estimated 14,080 deaths/year in US
  - Metastatic disease 12% 5 yr survival
  - Interleukin-2 durable cure in 7%
Checkpoint Blockade

Checkpoint Blockade @ NCI

- αCTLA-4, ipilimumab
- Phase I trial
- mAb (3mg/kg) + peptide
- Enrolled 14 patients
- 2 complete responders
- 1 partial response
- Accrual stopped for toxicity
  - Dermatitis, colitis, hepatitis, hypophysitis

Phan GQ 2003
Checkpoint Blockade

Checkpoint Blockade @ NCI

- Cautiously proceeded with Phase II trials in melanoma and RCC, initially with dose reduction (3 → 1 mg/kg)
- Objective response was associated with development of autoimmune events

**Melanoma, p=0.008**

<table>
<thead>
<tr>
<th></th>
<th>&gt; Gr 3 AE</th>
<th>&lt; Gr 3 AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response (CR = 2)</td>
<td>5 (36%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Non-responder</td>
<td>9</td>
<td>40</td>
</tr>
</tbody>
</table>

Attia P 2005

**RCC, p=0.009**

<table>
<thead>
<tr>
<th></th>
<th>&gt; Gr 3 AE</th>
<th>&lt; Gr 3 AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response (CR = 0)</td>
<td>5 (29%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Non-responder</td>
<td>12</td>
<td>23</td>
</tr>
</tbody>
</table>

Yang JC 2007
Checkpoint Blockade

Checkpoint Blockade @ NCI

- Formal Phase II intra-patient dose escalation demonstrated association of response with immune-related adverse events of any grade
- Enterocolitis was the most common grade 3/4 IRAE in patients with melanoma (18%) or RCC (28%)
- The administration of steroids to manage IRAE did not truncate responses

<table>
<thead>
<tr>
<th>Melanoma, p=0.0004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr 3/4 IRAE</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Objective Response (CR = 3)</td>
</tr>
<tr>
<td>14 (28%)</td>
</tr>
<tr>
<td>Non-responder</td>
</tr>
<tr>
<td>36</td>
</tr>
</tbody>
</table>

Beck KE 2006
Downey SG 2007
Checkpoint Blockade

Checkpoint Blockade @ NCI

- Developed algorithms for management of IRAEs
- Demonstrated durability of responses
  - OR 13-20%
  - 5 yr OS 13-23%
Checkpoint blockade

Checkpoint blockade in melanoma

nivolumab
pembrolizumab

anti-PD-1
PD-L1

anti-CTLA-4

ipilimumab

Tumour-specific T cell

PD-1

CTLA-4

CD28

B7

Antigen

MHC

T-cell receptor

Tumour cell or antigen-presenting cell

Drake C 2013
Ipilimumab

Ipilimumab for melanoma

- 11% response rate in Phase II trials at highest doses (10 mg/kg)
- Randomized Phase III ipilimumab ± gp100 vaccine vs. gp100 vaccine
- Allowed re-induction
- OR: ipilimumab arms 7% (38/540) CR in 3 patients
- Disease control rate 22%
- FDA approved for metastatic melanoma in March 2011

Hodi FS 2010
Ipilimumab for melanoma

- Updated survival
- 3 year OS, 20-26%
- "Tail of the curve"
  - Durable for a small # of patients

Schadendorf D 2015
Tremelimumab

- αCTLA-4
- 10% response rate in Phase II trials
- Randomized Phase III tremelimumab vs. dacarbazine/temozolomide
- No cross-over
- Failed to demonstrate survival advantage
- Currently being studied in combination trials

Ribas A 2013
Nivolumab

- αPD-1
- Phase I dose escalation
  - 0.1 mg/kg → 10 mg/kg
    - Melanoma (26/94, 28%)
    - NSCLC (14/76, 18%)
    - RCC (9/33, 27%)
    - CRPC (0/13)
    - CRC (0/19)
- Grade 3/4 toxicities in 6%
Nivolumab for melanoma

- Ipilimumab-refractory
- RCT: nivolumab vs chemotherapy of choice (CheckMate 037)
- Objective Response
  - Nivolumab 38/120, 31.7% with 4 CR
  - Chemotherapy 5/47, 10.6%

FDA approval for refractory melanoma in December 2014

Weber JS 2015
Nivolumab for melanoma

- Untreated metastatic disease
- Wildtype BRAF
- RCT: nivolumab vs dacarbazine (CheckMate 066)
- Objective response
  - Nivolumab 84/210 (40%)
    CR in 16 pts (7.6%)
  - Dacarbazine 29/208 (14%)
    CR in 2 pts (1%)

Robert C 2015
Nivolumab for melanoma

- Updated survival
- “Tail of the curve”

Overall Survival at 5 Years of Follow-up

34% 5 yr OS

Hodi F
(presented at AACR 2016)
Pembrolizumab for melanoma

- Ipilimumab-refractory
- Phase I, dose comparison (2mg/kg vs 10 mg/kg)
- 157 evaluable patients with OR 41 (26%), CR in 2 pts
- Disease control rate 50%
- Grade 3/4 AE 12%

**FDA approval for refractory melanoma in September 2014**
Pembrolizumab for melanoma

- Ipilimumab-refractory
- Phase II, dose comparison (2mg/kg vs 10 mg/kg) vs chemo
- 540 patients
  - 2mg/kg ORR 38 (21%), 10 mg/kg ORR 46 (25%), chemo 8 (4%)
- Grade 3/4 AE 12%

Weber JS 2015
Pembrolizumab for melanoma

Pembrolizumab for melanoma

- RCT, KEYNOTE-006, first-line therapy
- Pembrolizumab (q2w, q3w) vs ipilimumab
- 1:1:1
- 834 patients
- Objective Response
  - Pembrolizumab q2w 94/279 (33.7%), CR 14
  - Pembrolizumab q3w 91/277 (32.9%), CR 17
  - Ipilimumab 33/278 (11.9%), CR 4

Robert C 2015
Pembrolizumab for melanoma

- Grade ≥3 AE
  - Pembrolizumab q2w 13.3% (1.4% Colitis)
  - Pembrolizumab q3w 10.1% (2.5% Colitis)
  - Ipilimumab 19.9% (7% Colitis)
Pembrolizumab for melanoma

• Updated survival
• "Tail of the curve"
Checkpoint modulation

Checkpoint Modulation

In melanoma, the two approved antibodies interfere with separate receptor/ligand complexes

Could combination therapy improve response or survival?
Nivolumab/Ipilimumab

Nivolumab/Ipilimumab for melanoma

- Previously untreated
- Phase III, RCT
- 945 patients
- 1:1:1
- PD-L1 (+) ≥5%

Table 1. Characteristics of the Patients at Baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nivolumab (N = 316)</th>
<th>Nivolumab plus Ipilimumab (N = 314)</th>
<th>Ipilimumab (N = 315)</th>
<th>Total (N = 945)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>80 (25.3)</td>
<td>68 (21.7)</td>
<td>75 (23.8)</td>
<td>223 (23.6)</td>
</tr>
<tr>
<td>Negative</td>
<td>208 (65.8)</td>
<td>210 (66.9)</td>
<td>202 (64.1)</td>
<td>620 (65.6)</td>
</tr>
<tr>
<td>Could not be determined or evaluated</td>
<td>28 (8.9)</td>
<td>36 (11.5)</td>
<td>38 (12.1)</td>
<td>102 (10.8)</td>
</tr>
<tr>
<td>BRAF status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation</td>
<td>100 (31.6)</td>
<td>101 (32.2)</td>
<td>97 (30.8)</td>
<td>298 (31.5)</td>
</tr>
<tr>
<td>No mutation</td>
<td>216 (68.4)</td>
<td>213 (67.8)</td>
<td>218 (69.2)</td>
<td>647 (68.5)</td>
</tr>
</tbody>
</table>

Larkin J 2015
Nivolumab/Ipilimumab

Nivolumab/Ipilimumab for melanoma

- Previously untreated
- Phase III, RCT
- 945 patients
- 1:1:1

- Grade 3/4 AE
  - Nivolumab 16.3%
  - Ipilimumab 27.3%
  - Combo 55.0%

Table 2. Response to Treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nivolumab (N = 316)</th>
<th>Nivolumab plus Ipilimumab (N = 314)</th>
<th>Ipilimumab (N = 315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response — no. (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>28 (8.9)</td>
<td>36 (11.5)</td>
<td>7 (2.2)</td>
</tr>
<tr>
<td>Partial response</td>
<td>110 (34.8)</td>
<td>145 (46.2)</td>
<td>53 (16.8)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>34 (10.8)</td>
<td>41 (13.1)</td>
<td>69 (21.9)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>119 (37.7)</td>
<td>71 (22.6)</td>
<td>154 (48.9)</td>
</tr>
<tr>
<td>Could not be determined</td>
<td>25 (7.9)</td>
<td>21 (6.7)</td>
<td>32 (10.2)</td>
</tr>
<tr>
<td>Objective response†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with response</td>
<td>138</td>
<td>181</td>
<td>60</td>
</tr>
<tr>
<td>% of patients (95% CI)</td>
<td>43.7 (38.1–49.3)</td>
<td>57.6 (52.0–63.2)</td>
<td>19.0 (14.9–23.8)</td>
</tr>
<tr>
<td>Estimated odds ratio (95% CI)‡</td>
<td>5.40 (2.02–13.72)</td>
<td>6.11 (3.99–10.38)</td>
<td>—</td>
</tr>
<tr>
<td>Two-sided P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>—</td>
</tr>
<tr>
<td>Time to objective response — mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.78</td>
<td>2.76</td>
<td>2.79</td>
</tr>
<tr>
<td>Range</td>
<td>2.3–12.5</td>
<td>1.1–11.6</td>
<td>2.5–12.4</td>
</tr>
</tbody>
</table>

* The best overall response was assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors, version 1.1.
† Data included patients with a complete response and those with a partial response. The calculation of the confidence interval was based on the Clopper–Pearson method. These analyses were conducted with the use of a two-sided Cochran–Mantel–Haenszel test stratified according to PD-L1 status, BRAF mutation status, and metastasis stage.
‡ The comparison is with the ipilimumab group.

Larkin J 2015
## Nivolumab/Ipilimumab for melanoma

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Nivolumab + Ipilimumab</th>
<th>Ipilimumab</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall ORR</strong></td>
<td>43.7%</td>
<td>57.6%</td>
<td>19.0%</td>
<td>40.1%</td>
</tr>
<tr>
<td><strong>PD-L1 (+)</strong></td>
<td>46/80</td>
<td>49/68</td>
<td>16/75</td>
<td>111/223</td>
</tr>
<tr>
<td></td>
<td>57.5%</td>
<td>72.1%</td>
<td>21.3%</td>
<td>49.8%</td>
</tr>
<tr>
<td><strong>PD-L1 (-)</strong></td>
<td>86/208</td>
<td>115/210</td>
<td>36/202</td>
<td>237/620</td>
</tr>
<tr>
<td></td>
<td>41.3%</td>
<td>54.8%</td>
<td>17.8%</td>
<td>38.2%</td>
</tr>
<tr>
<td><strong>PD-L1 unknown</strong></td>
<td>6/28</td>
<td>17/36</td>
<td>8/38</td>
<td>31/102</td>
</tr>
<tr>
<td></td>
<td>21.4%</td>
<td>47.2%</td>
<td>21.1%</td>
<td>30.3%</td>
</tr>
</tbody>
</table>

Larkin J 2015
Nivolumab/ipilimumab for melanoma

-updated results-

Progression-Free Survival (Intent-to-Treat Population)

- Minimum follow-up of 18 months
- Overall survival not updated, still immature

FDA approval of combination for melanoma in January 2016

Wolchok (presented at ASCO 2016)
Melanoma

Why melanoma?

Highly mutated tumors

- Non-small cell lung cancer
  - ~158,040 deaths/year in US
- Regional disease
  - 16% 5 yr survival
- Metastatic disease
  - 2% 5 yr survival
- Correlation between smoking and # mutations
- Tumors with mismatch repair (MMR) deficiency
  - Lynch syndrome (germline mutation)
  - Sporadic mutation
  - MSH2, MLH1, MSH6, PMS2
- Bladder cancer
  - 16,000 deaths/year in US
  - Highly lethal once metastatic
Nivolumab for NSCLC

- NSCLC refractory to ≥ 2 treatments
- Phase II (CheckMate 063)
- 3 mg/kg q2w until progression or toxicity
- 117 patients treated
- Objective Response 17 (14.5%), no CR

Rizvi NA 2015
Nivolumab for NSCLC

• RCT
• Nivolumab vs docetaxel
• Refractory to one platinum-based regimen
• Objective Response
  – Nivolumab 27/135 (20%)
  – Docetaxel 12/137 (9%)

FDA approval for refractory NSCLC in March 2015

Brahmer 2015
Nivolumab for NSCLC

- Nivolumab vs docetaxel
- Objective Response
  - Nivolumab 56/292 (19%)
  - Docetaxel 36/290 (12%)

FDA approval for refractory non-squamous NSCLC in October 2015

Borghaei 2015
Pembrolizumab for NSCLC

- 495 patients, subset of KEYNOTE 001
- Wide range of inclusion criteria
  - 94 treatment naïve patients
  - 126 never smokers
  - 401 nonsquamous
- Majority at 10 mg/kg either q2w or q3w
- Objective response 96/495 (19.4%)
  - Never smokers 13/126 (10.3%)
  - Former/current 83/369 (22.5%)
- Grade ≥3 AE
  - Dyspnea 3.8%
  - Pneumonitis 1.8% including a fatality

FDA decision to be made
October 2, 2015

Garon EB 2015
antiPD-L1

αPD-L1 in Urothelial bladder cancer

- MPDL3280A
- Atezolizumab
- 15 mg/kg q3w
- 27% tumors with >5% PD-L1 by IHC
- 65 patients with pre-treatment biopsy
- Objective Response
  - ≥ 5% PD-L1 13/30 (43.3%)
  - < 5% PD-L1 4/35 (11.4%)
- Grade 3/4 AE 4%

FDA approval for urothelial cancer in May 2016

Powles T 2014
αPD-L1 in Urothelial bladder cancer

- 310 patients
- Objective Response
  - 45 (15%)
  - With 15 complete responses
- Overall Survival
  - 7.9 months
- 1 yr Survival
  - 37%
Urothelial Cancer

Pembrolizumab in Urothelial Cancer

- Part of KEYNOTE-012
- Required ≥ 1% PD-L1 staining (61/95, 64.2%)
- 10 mg/kg q2w
- 33 patients (29 eval)
- OR 27.6%, CR 10.3% (3 pts)
- Grade ≥ 3 AE 15%

Abstract: Plimack E 2015
Nivolumab in Urothelial Cancer

- One cohort of a larger study, 3 mg/kg q2w
- Did not require ≥ 1% PD-L1 staining (25/67, 37%)
- 78 patients (29 eval)
- OR 24.4%, CR 6.4% (5 pts), Grade ≥ 3 AE 22%
MMR-deficient cancer

Pembrolizumab for MMR-deficient cancer

- Builds on hypothesis of neoantigens from somatic mutations
- Phase 2 study
- Three parallel cohorts
  - MMR-proficient CRC
  - MMR-deficient CRC
  - MMR-deficient other

Le DT 2015
Tumor-stromal interface

Pembrolizumab at the tumor-stroma interface

Le DT 2015
Nivolumab for highly mutated colorectal cancer

- CheckMate 142
- dMMR or microsatellite instability-high (MSI-H)
- 53 patients verified dMMR/MSI-H
- OR 36% (19/53)
- CR 2% (1/53)

FDA approval for dMMR/MSI-H tumors in July 2017

Overman MJ 2017
THE LANCET Oncology
Checkpoint blockade

Checkpoint Blockade

- Highly mutated tumors
  - Melanoma
  - Non-small cell lung cancer
  - Bladder cancer
  - Tumors with mismatch repair deficiency
- Use in other tumors?
  - Renal cell
    - Responds to other immunotherapy
  - Hodgkin’s lymphoma
    - Reed-Sternberg cells have elevated amounts of PD-L1
  - Head and neck SCC
    - HPV and mutations
Renal cell cancer

Nivolumab for renal cell cancer

- Nivolumab vs everolimus
- Objective Response
  - Nivolumab 103/410 (25%)
  - Everolimus 22/411 (5%)
- Median Survival
  - Nivolumab 25.0 months
  - Everolimus 19.6 months

FDA approval for renal cell carcinoma in November 2015

Motzer 2015
Hodgkin’s lymphoma

Nivolumab for Hodgkin’s Lymphoma

- 80 patients
  - Refractory to stem cell transplant
  - Refractory to brentuximab

- Objective Response
  - 53/80 (66%)
  - 7 complete remission

FDA approval for refractory cHL in May 2016

Younes A 2016

THE LANCET Oncology
Pembrolizumab in Head and Neck SCC

**Progression-Free Survival**
- Median (95% CI), 2 months (1.9–2.1)
- 6-month, 25%
- 12-month, 17%

**Overall Survival**
- Median (95% CI), 8 months (6–10)
- 6-month, 58%
- 12-month, 38%

**FDA approval for recurrent or metastatic head and neck squamous carcinoma in August 2016**

Mehra R, presented 2016
Avelumab

Avelumab in Merkel cell carcinoma

- 88 patients
  - Confirmed metastatic disease
- Objective Response
  - 28/88 (32%)
  - 8 complete remission

FDA approval for Merkel cell carcinoma in March 2017

Kaufman HL 2016

THE LANCET Oncology
### PD-1/PD-L1 pathway

#### Blocking the PD-1/PD-L1 pathway

<table>
<thead>
<tr>
<th>Drug</th>
<th>Melanoma</th>
<th>NSCLC</th>
<th>RCC</th>
<th>Bladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-PD-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>32% (n=107)</td>
<td>17% (n=129)</td>
<td>29% (n=34)</td>
<td>NR</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>38% (n=135)</td>
<td>26% (n=42)</td>
<td>24% (n=29)</td>
<td></td>
</tr>
<tr>
<td>Anti-PD-L1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS-936559</td>
<td>17% (n=52)</td>
<td>10% (n=49)</td>
<td>12% (n=17)</td>
<td>NR</td>
</tr>
<tr>
<td>MEDI4736</td>
<td>NR</td>
<td>16% (n=58)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>30% (n=43)</td>
<td>23% (n=53)</td>
<td>14% (n=56)</td>
<td>26% (n=65)</td>
</tr>
</tbody>
</table>

**FDA Approved (As of 9/2016)**

Adapted from Lipson 2015
## PD-1/PD-L1 blockade in mBrCa

<table>
<thead>
<tr>
<th>Trial Characteristics</th>
<th>PD-L1 Status</th>
<th>Drug</th>
<th>Author</th>
<th>Ref.</th>
<th>n</th>
<th>OR (%)</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-12 mTNBC</td>
<td>PD-L1+ (≥1%)</td>
<td>pembrolizumab</td>
<td>Nanda</td>
<td>JCO 2016</td>
<td>27</td>
<td>5 (18.5%)</td>
<td>1</td>
</tr>
<tr>
<td>KEYNOTE-28 ER+/Her2-</td>
<td>PD-L1+ (≥1%)</td>
<td>pembrolizumab</td>
<td>Rugo</td>
<td>SABCS 2015</td>
<td>25</td>
<td>3 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>KEYNOTE-86 Cohort A mTNBC (refractory)</td>
<td>N/A</td>
<td>pembrolizumab</td>
<td>Adams</td>
<td>ASCO 2017</td>
<td>170</td>
<td>8 (4.7%)</td>
<td>1</td>
</tr>
<tr>
<td>KEYNOTE-86 Cohort B mTNBC (1st line)</td>
<td>PD-L1+ (≥1%)</td>
<td>pembrolizumab</td>
<td>Adams</td>
<td>ASCO 2017</td>
<td>52</td>
<td>12 (23%)</td>
<td>2</td>
</tr>
<tr>
<td>JAVELIN Phase Ib Subgroup: mTNBC Sub-subgroup: PD-L1+</td>
<td>N/A (≥10%)</td>
<td>avelumab</td>
<td>Dirix</td>
<td>SABCS 2016*</td>
<td>168</td>
<td>8 (4.8%)</td>
<td>1</td>
</tr>
<tr>
<td>mTNBC Subgroup: 1st line Subgroup: PD-L1+</td>
<td>N/A (≥5%)</td>
<td>atezolizumab</td>
<td>Schmid</td>
<td>AACR 2017</td>
<td>112</td>
<td>11 (10%)</td>
<td>3</td>
</tr>
</tbody>
</table>

N/A: accepted patients regardless of PD-L1 status

* Initial data presented by Dirix, updated in material requested from EMD/Serrano
Pembrolizumab in Gastric Cancer

- Part of KEYNOTE-012
- Required ≥ 1% PD-L1 staining (65/162, 40%)
- 10 mg/kg q2w
- 39 patients
- OR 22%
- Grade ≥ 3 AE 10%
**PD-1/PD-L1 blockade**

### PD-1/PD-L1 blockade at ASCO 2016/7

<table>
<thead>
<tr>
<th>Disease</th>
<th>Drug</th>
<th>Author</th>
<th>n</th>
<th>OR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoma</td>
<td>nivolumab</td>
<td>Paoluzzi</td>
<td>14</td>
<td>3 (21%)</td>
<td>0</td>
</tr>
<tr>
<td>Uterine leiomyosarcoma</td>
<td>nivolumab</td>
<td>George</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>nivo3</td>
<td>Antonia</td>
<td>98</td>
<td>10 (10%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>nivo1+ipi3</td>
<td></td>
<td>61</td>
<td>14 (23%)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>nivo3+ipi1</td>
<td></td>
<td>54</td>
<td>10 (19%)</td>
<td>0</td>
</tr>
<tr>
<td>Salivary gland cancer</td>
<td>pembrolizumab</td>
<td>Cohen</td>
<td>26</td>
<td>3 (11.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>pembrolizumab</td>
<td>Frenel</td>
<td>24</td>
<td>4 (17%)</td>
<td>0</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>pembrolizumab</td>
<td>Ott</td>
<td>24</td>
<td>3 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>pembrolizumab</td>
<td>Doi</td>
<td>23</td>
<td>7 (30%)</td>
<td>0</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>pembrolizumab</td>
<td>Mehnert</td>
<td>22</td>
<td>2 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Gastric/GEJ</td>
<td>avelumab</td>
<td>Chung</td>
<td>151</td>
<td>14 (9%)</td>
<td>2</td>
</tr>
<tr>
<td>Adrenocortical cancer</td>
<td>avelumab</td>
<td>Le Tourneau</td>
<td>37</td>
<td>2/19 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>avelumab</td>
<td>Disis</td>
<td>124</td>
<td>12 (9.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>avelumab</td>
<td>Hassan</td>
<td>53</td>
<td>5 (9.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatocellular (liver) cancer</td>
<td>durvalumab</td>
<td>Wainberg</td>
<td>39</td>
<td>4 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>durvalumab</td>
<td>Reardon</td>
<td>30</td>
<td>4 (13%)</td>
<td>0</td>
</tr>
</tbody>
</table>
Checkpoint modulation

Questions?