Immune checkpoint Blockade

NCI CCR TRACO
Stephanie L. Goff, MD
September 14, 2016
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
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
T cell activation

- Signal 1: Specificity
- TCR engages antigen in context of MHC
T cell activation

• Signal 2: Activation vs. Anergy
T cell activation

- **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
CTLA-4

CTLA-4

- 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 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%

Smith FO Clin Cancer Res 2008

Klapper JA Cancer 2008

American Cancer Society Facts and Figures 2015
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 inpatient 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

**Melanoma, p=0.0004**

<table>
<thead>
<tr>
<th></th>
<th>Gr 3/4 IRAE</th>
<th>Gr 1/2 IRAE</th>
<th>No IRAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CR = 3)</td>
<td>14 (28%)</td>
<td>8 (22%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Non-responder</td>
<td>36</td>
<td>28</td>
<td>52</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%

Clinical Cancer Research

Prieto PA 2012
Checkpoint blockade

Checkpoint blockade in melanoma

Drake C 2013
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

Ipilimumab for melanoma

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

Schadendorf D 2015
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%

Topalian SL 2010
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%)
Nivolumab for melanoma

- Updated survival
- “Tail of the curve”

**Overall Survival at 5 Years of Follow-up**

- All Patients (events: 69/107), median and 95% CI: 17.3 (12.5–37.8)
- NIVO 3 mg/kg (events: 11/17), median and 95% CI: 20.3 (7.2–NR)

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

Robert C 2014
THE LANCET
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 $\geq 3$ 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"

Ribas A 2016
Checkpoint modulation

Checkpoint Modulation

- In melanoma, the two approved antibodies interfere with separate receptor/ligand complexes
- Could combination therapy improve response or survival?

Topalian, Cancer Cell 2015
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 — no. (%)</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 — no. (%)</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%

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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>
</tbody>
</table>

| Objective response               |                      |                                     |                       |
| No. of patients with response    | 138                   | 181                                  | 60                    |
| % of patients (95% CI)           | 43.7 (38.1–49.3)      | 57.6 (52.0–63.2)                     | 19.0 (14.9–23.8)      |
| Estimated odds ratio (95% CI)‡  | 3.40 (2.02–5.72)      | 6.11 (3.39–10.38)                    | —                     |
| Two-sided P value                | <0.001                | <0.001                               | —                     |
| Time to objective response — mo | 2.78                  | 2.76                                 | 2.79                  |
| Median                           | 2.3–12.5              | 1.1–11.6                             | 2.5–12.4              |
| Range                            |                      |                                     |                       |

* 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-

- 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

nature
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
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
Tumor-stromal interface

Pembrolizumab at the tumor-stroma interface

Le DT 2015
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
Head and Neck SCC

Pembrolizumab in Head and Neck SCC

- Part of KEYNOTE-012
- No requirement for PD-L1 expression
- 200mg q3w
- 192 patients, HPV+ 45/192 (23%)

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Total N = 192†</th>
<th>HPV+ n = 45‡</th>
<th>HPV− n = 147‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>ORR</td>
<td>34</td>
<td>18</td>
<td>13–24</td>
</tr>
<tr>
<td>CR</td>
<td>8</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>PR</td>
<td>26</td>
<td>14</td>
<td>–</td>
</tr>
<tr>
<td>SD</td>
<td>33</td>
<td>17</td>
<td>–</td>
</tr>
<tr>
<td>PD</td>
<td>93</td>
<td>48</td>
<td>–</td>
</tr>
<tr>
<td>NA§</td>
<td>32</td>
<td>17</td>
<td>–</td>
</tr>
</tbody>
</table>

Mehra R, presented 2016
Pembrolizumab

Pembrolizumab in Head and Neck SCC

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

Mehra R, presented 2016
## 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><strong>Anti-PD-1</strong></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>NR</td>
<td>24% (n=29)</td>
</tr>
<tr>
<td><strong>Anti-PD-L1</strong></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
Pembrolizumab in Breast Cancer

- Part of KEYNOTE 012
- Triple Negative BC
- PD-L1 (+) on IHC (65/111, 59%)
- 10mg/kg q2w
- 32 patients (27 evaluable)
- OR 18.5%, CR 3.7% (1 pt)
- Grade ≥ 3 AE 9.4%

- TNBC
- PD-L1 (+) on IHC (20/105, 19%)
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%
Anti-PD-L1 in melanoma

- MPDL3280A
- Estimated prevalence of PD-L1 staining 40%
- Immune-related Grade 3/4 AE in 2 patients (5%)
Trimelimumab

- 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
Checkpoint pipeline

Pardoll D 2012
Checkpoint modulation

Questions?