Cancer Immunotherapy Patient Forum

for the Treatment of Melanoma, Leukemia, Lymphoma, Lung and Genitourinary Cancers - November 7, 2015
The Current Role of Immunotherapy in the Treatment of Patients with Cancer

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Georgetown-Lombardi Comprehensive Cancer Center

November 7, 2015
Conflicts of Interest

Consultant:
Genentech/Roche, BMS, Merck, Nectar, Novartis, Pfizer, Caladrius, Amgen, Alkermes

Advisory Board:
X4Pharma, Caladrius, Merck, Novartis
We Have Been at War Against Cancer Throughout Human History

President Nixon declares a "War on Cancer" in 1971

Medieval Saxon man with a large tumor of the left femur
The “War on Cancer” is fought one person at a time…

- **Primary Combatants:**
  - Malignant cell population
  - Host immune system

- The host immune system is the dominant active enemy faced by a developing cancer

- All “successful” cancers must solve the challenges of overcoming defenses erected by host immune systems
Successful Cancers Escape (Solve the Challenge of Host Immunity) in Different Ways

- **Overwhelm** – out-proliferate the immune response
- **Hide** – decreased antigen or MHC Class I or II expression
- **Subvert** – immunosuppressive chemokines, cytokines
- **Shield** – exclude infiltration by tumor antigen-reactive T cells
- **Defend** – deactivate tumor-targeting T cells that attack tumor cells

Weiner L, SITC Symposium 8/7/2015
Cancer Immunotherapy

- Treatment of disease by inducing, enhancing, or suppressing an immune response

- “Treating the immune system so it can treat the cancer” (J. Wolchok)

- Immunotherapy can cure cancers
Most Cancers Have Mutations

Mutated proteins represent potential antigens – targets for immune recognition and destruction

Lawrence, Nature 499:214 2013
Tumor Immunology: Overview

1. Tumor antigen
2. Lymph node
3. Dendritic cell

- Tumor antigen
- Dendritic cell
- MHC
- B7
- TCR
- CD28
- TCR
- CD28

- Activated T cell
- Resting T cell
- Cytokines (IL-2)
- Perforin granzyme

- T-cell clonal expansion
HD IL-2 Therapy: Durable Responses

- HD IL-2 produces durable responses in ~10% of patients with advanced melanoma or RCC
- Few relapses in patients responding for over 2.5 years (likely cured)
- FDA approval in 1992 (RCC) and 1997 (melanoma)

High-Dose IL-2 Therapy: 30-year History

- High-dose IL-2 appears to benefit pts, but:
  - Toxic, complex; must be delivered as an inpatient regimen
- Use remained limited to selected pts treated at experienced centers
- Efforts to develop more tolerable regimens unsuccessful
- Efforts to better select pts who might benefit from high-dose IL-2 therapy produced modest advances
- Proof of principle that immunotherapy can produce durable benefit in pts with cancer, but newer immunotherapies are needed
Non-inflamed Tumor Phenotype

- Poor effector cell trafficking due to:
  - Low inflammation and chemokine expression

- Poor effector cell function due to:
  - Hypoxia and high expression of vascular markers, macrophages, fibroblasts

Inflamed Tumor Phenotype

- T cell recruitment
  - High levels of innate immune signals
  - Chemokine expression
- Nevertheless, negative immune regulators dominate
  - Inhibitory receptors
  - Suppressive cells
  - Suppressive enzymes (IDO, arginase)

Studies suggest these are the tumors that can respond to Immunotherapy

Inflamed Tumor Phenotype

- T cell recruitment
  - High levels of innate immune signals
  - Chemokine expression
- Nevertheless, negative immune regulators dominate
- TIL therapy: remove anti-tumor T cells from immunosuppressive environment, select/expand ex vivo then re-administer

Tumor-Infiltrating Lymphocytes + IL-2 in Metastatic Melanoma: OS

Dampening the Immune System in Cancer

Priming Phase

Effector Phase

Blocking Immunologic Checkpoints

Priming:
T-Cell Activation in the Lymph Node

Dendritic cell

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 |

Schadendorf D, J Clin Oncol 2015.
Blocking Immunologic Checkpoints

Clinical Development of Inhibitors of PD-1 Immune Checkpoint

<table>
<thead>
<tr>
<th>Target</th>
<th>Antibody</th>
<th>Molecule</th>
<th>Company</th>
<th>Development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1</td>
<td>Nivolumab (Opdivo)</td>
<td>Fully human IgG4</td>
<td>Bristol-Myers Squibb</td>
<td>Approved in Melanoma, NSCLC etc</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab (Keytruda)</td>
<td>Humanized IgG4</td>
<td>Merck</td>
<td>Approved in Melanoma, NSCLC etc</td>
</tr>
<tr>
<td></td>
<td>Pidilizumab</td>
<td>Humanized IgG1</td>
<td>Curetech Medivation</td>
<td>Phase II Melanoma, Heme Malignancies</td>
</tr>
<tr>
<td>PD-L1</td>
<td>Durvalumab</td>
<td>Engineered human IgG1</td>
<td>MedImmune</td>
<td>Phase I-II multiple tumors</td>
</tr>
<tr>
<td></td>
<td>Atezolizumab</td>
<td>Engineered human IgG1</td>
<td>Genentech</td>
<td>Phase III in bladder, RCC, NSCLC</td>
</tr>
<tr>
<td></td>
<td>Avelumab</td>
<td>Fully human IgG1</td>
<td>EMD Serono (Pfizer)</td>
<td>Phase II in ovarian, Phase I in multiple solid tumors</td>
</tr>
</tbody>
</table>
## Nivolumab: Clinical Activity

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Dose, mg/kg</th>
<th>ORR (CR/PR), n (%)</th>
<th>SD ≥ 24 Wks, n (%)</th>
<th>Median PFS, Mos</th>
<th>MedianOS, Mos</th>
<th>1 yr, %</th>
<th>2 yr, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEL (n = 107)</td>
<td>0.1-10</td>
<td>32 (34)</td>
<td>7 (7)</td>
<td>3.7</td>
<td>17.3</td>
<td>68</td>
<td>48</td>
</tr>
<tr>
<td>NSCLC (n = 129)</td>
<td>1-10</td>
<td><strong>22 (17)</strong></td>
<td><strong>13 (10)</strong></td>
<td>2.3</td>
<td>9.9</td>
<td>42</td>
<td>24</td>
</tr>
<tr>
<td>RCC (n = 34)</td>
<td>1 or 10</td>
<td>10 (29)</td>
<td>9 (27)</td>
<td>7.3</td>
<td>&gt; 22</td>
<td>70</td>
<td>50</td>
</tr>
</tbody>
</table>

Will need updating from ASCO 2014 reports.

Mel - Abst 9002
NSCLC - Abst 8112
Author, 7/14/2014
Pembrolizumab: Time to Response and On-Study Duration

Presented by: Antoni Ribas

Ongoing response defined as alive, progression free, and without new anticancer therapy.

Pembrolizumab received FDA approval for melanoma 9/4/14

*Ongoing response defined as alive, progression free, and without new anticancer therapy.*
Design - please format with our style
Author, 6/24/2014
Nivo 037 Study: Time and Duration of Response

36/38 (95%) of nivolumab responses ongoing with minimum follow-up of 24 weeks in all patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median time to response, (range), mo</th>
<th>Median duration of response, (range), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>2.1 (1.6, 7.4)</td>
<td>NR (1.4+, 10.0+)</td>
</tr>
<tr>
<td>ICC</td>
<td>3.5 (2.1, 6.1)</td>
<td>3.6 (1.3+, 3.5)</td>
</tr>
</tbody>
</table>

Nivolumab received FDA approval for melanoma 12/21/14

"+" denotes patients who are censored (still in response);
NR = not reached

Data report date: 30 Apr 2014
Spectrum of PD-1/PD-L1 Antagonist Activity

**Active**
- **Melanoma**
- **Renal cancer (clear cell and non-clear cell)**
- **NSCLC – adenocarcinoma and Squamous cell**
- Small cell lung cancer
- **Head and neck cancer**
- Gastric and GE junction
- **Mismatch repair deficient tumors (colon, cholangiocarcinoma)**
- **Bladder cancer**
- Triple negative breast cancer
- Ovarian cancer
- Glioblastoma
- Hepatocellular carcinoma
- Thymic carcinoma
- Mesothelioma
- Cervical cancer
- **Hodgkin Lymphoma**
- Diffuse large cell lymphoma
- Follicular lymphoma
- T-cell lymphoma (CTCL, PTCL)
- **Merkel Cell**

8 for 8 Phase III Trials

**Minimal to no activity:**
- Prostate cancer
- MMR+ Colon cancer
- Myeloma
- Pancreatic Cancer
- ER+ breast cancer
Randomized phase III trials of nivolumab vs. docetaxel in NSCLC

**Trial 17: Squamous Cell Carcinoma**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab n = 135</th>
<th>Docetaxel n = 137</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS mos.</td>
<td>9.2 (7.3, 13.3)</td>
<td>6.0 (5.1, 7.3)</td>
</tr>
<tr>
<td># events</td>
<td>86</td>
<td>113</td>
</tr>
<tr>
<td>HR</td>
<td>0.59 (0.44, 0.79)</td>
<td>0.00025</td>
</tr>
</tbody>
</table>

Nivolumab received FDA approval on 3/4/15 in 2nd line Squamous NSCLC.

**Trial 57: Non-Squamous Cell Carcinoma**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab N = 292</th>
<th>Docetaxel N = 290</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, mo</td>
<td>12.2</td>
<td>9.4</td>
</tr>
<tr>
<td>HR</td>
<td>0.73 (0.59, 0.89)</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

Nivolumab received FDA approval on 10/1/15 in 2nd line non-Squamous NSCLC.
Pembrolizumab Monotherapy for NSCLC: Efficacy Data Supporting the Approved Indication

KEYTRUDA is indicated for the treatment of:

- Patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy
- Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA

FDA Approval with companion biomarker 10/2015

<table>
<thead>
<tr>
<th>Overall Response Rate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR%, (95% CI)</td>
<td>41% (29, 54)</td>
</tr>
<tr>
<td>Complete Response</td>
<td>0%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>41%</td>
</tr>
</tbody>
</table>

Keytruda (pembrolizumab) Prescribing Information. Whitehouse Station, NJ: Merck & Co, Inc; October 2015.
Nivolumab RCC Ph3: Overall Survival

Median OS, months (95% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Median OS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (N = 410)</td>
<td>410</td>
<td>25.0</td>
<td>21.8–NE</td>
</tr>
<tr>
<td>Everolimus (N = 411)</td>
<td>411</td>
<td>19.6</td>
<td>17.6–23.1</td>
</tr>
</tbody>
</table>

HR (98.5% CI), 0.73 (0.57–0.93)  
\( P = 0.0018 \)

Minimum follow-up was 14 months

CI, confidence interval; HR, hazard ratio; NE, not estimable.
Atezolizumab: Tumor Burden Over Time in Urothelial Bladder Cancer

- Median duration of response has not been reached
  - 0.1+ to 30.3+ weeks IHC (IC) 2 or 3
  - 0.1+ to 6.0+ weeks for IHC (IC) 0 or 1


FDA Breakthrough Designation
**IMvigor 210: Efficacy**

*Changes in Target Lesions by PD-L1 Subgroup*

111/258 (43%) patients with tumor assessments had SLD reduction

SLD, sum of longest diameters. *a* > 100% increase. *b* Per confirmed RECIST v1.1 (independent review).

Data cutoff May 5, 2015. Follow up ≥ 24 weeks. Patients without post-baseline tumor assessments not included.

Several patients with CR had < 100% reduction due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.

Rosenberg JE, et al.: IMvigor 210: Phase II Atezolizumab in mUC
Phase Ib KEYNOTE-12 Pembrolizumab Study: SCCHN Cohort

- N = 132 patients with recurrent or metastatic SCCHN (HPV+ or HPV-)
- ORR: 25% with 1 CR and 28 PRs

No permission yet.
Author, 6/11/2015
Most Cancers Have Mutations

Mutated proteins represent potential antigens – targets for immune recognition and destruction

Tumors with more mutations appear more likely to respond to PD1 blockade

*Lawrence, Nature 499:214 2013*
# 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>

Nivolumab in Relapsed/Refractory Hodgkin Lymphoma

- 23 pts / double refractory (ASCT and brentuximab)
- Nivolumab 3 mg/kg q2 wks until POD / toxicity up to 2y max
- 20/23 resp: **ORR 78% / 17% CR** (3 others had SD)
- 2y PFS 86% ++
- Well tolerated

Ansell, NEJM; Jan 2015
Amplification PDL1 and/or PDL2 (ligands for PD1) at 9p24.1

Overexpression PDL1 or PDL2 in RS cells

Highlight the importance of the PD-1 immune evasion pathway with structural basis

Ansell, NEJM; Jan 2015
Summary of PD-1/PD-L1 Blockade Immune-Mediated Toxicities

- Fatigue
- Rash: maculopapular and pruritus
  - Topical treatments
- Diarrhea/colitis
- Hepatitis/liver enzyme abnormalities
- Infusion reactions
- Endocrinopathies: thyroid, adrenal, hypophysitis
- Pneumonitis
- Grade 3/4 toxicities uncommon

Single Agent Anti-PD1/PDL1 Blockade: Current and Future Directions

- Determine treatment length
- Adjuvant protocols (melanoma, others?)
- Combinations:
  - Immunotherapy, targeted therapy, RT, Vaccines
- Biomarker refinement
Ipilimumab + Nivolumab: Change in Target Lesions

Cohort 2: 1 mg/kg nivolumab + 3 mg/kg ipilimumab

<table>
<thead>
<tr>
<th>Therapy, %</th>
<th>ORR</th>
<th>≥ 80% Tumor Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>A1</td>
<td>10</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>A2</td>
<td>28</td>
</tr>
<tr>
<td>Combination (cohort 2)</td>
<td>A7</td>
<td>53</td>
</tr>
</tbody>
</table>

A1 Please verify. I could not confirm these numbers. ORR from ipilimumab was 11% per ASCO presentation slide and >80% tumor reduction was "<10%"
Author, 5/12/2014

A2 Please verify. I could not confirm these numbers. ORR from nivolumab was 41% per ASCO presentation slide and >80% tumor reduction was "<10%"
Author, 5/12/2014

A7 Perhaps the data from the ipilimumab and nivolumab monotherapy rows are from another source?
Author, 5/13/2014

A3 Data to be updated at ASCO 2014
Author, 5/21/2014
Nivo-Ipi vs Ipi alone

HR 0.40 (95% CI, 0.23, 0.68; \( P < 0.001 \))

Death or disease progression, n/N

<table>
<thead>
<tr>
<th></th>
<th>Death or disease progression, n/N</th>
<th>Median PFS, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO + IPI</td>
<td>30/72</td>
<td>NR</td>
</tr>
<tr>
<td>IPI monotherapy</td>
<td>25/37</td>
<td>4.4 (2.8-5.7)</td>
</tr>
</tbody>
</table>

Response rates

Nivo-mpi 61%
Ipi alone 10%

Postow et al NEJM, 2015
Nivo-Ipi vs Ipi alone

FDA Approved for BRAF WT Melanoma 10/1/15

Response rates
Nivo-mpi 61%
Ipi alone 10%

Postow et al NEJM, 2015
Nivo vs Nivo + Ipi: Topline Melanoma Data

<table>
<thead>
<tr>
<th></th>
<th>Nivo</th>
<th>Nivo + Ipi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med PFS (months)</td>
<td><strong>6.9</strong> (4.3-9.5)</td>
<td><strong>11.5</strong> (8.9-16.7)</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td><strong>43.7</strong> (38.1-49.3)</td>
<td><strong>57.6</strong> (52.0-63.2)</td>
</tr>
<tr>
<td>CR %</td>
<td>8.9</td>
<td>11.5</td>
</tr>
<tr>
<td>Tumor Burden change</td>
<td>- 34.5%</td>
<td>- 51.9%</td>
</tr>
<tr>
<td>Response Duration</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Med OS</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Grade 3-4 SAEs</td>
<td>16%</td>
<td>55%</td>
</tr>
</tbody>
</table>

Proof of principle that combination immunotherapy can produce greater activity than anti-PD1 alone.
Additional Issues/opportunities for Nivo + Ipi

- Transition into the community
- Less toxic regimen
  - Less Ipi (2 cycles; lower dose, less frequent)
  - Better toxicity management (more liberal immune suppression)
  - Substitute for Ipi (many options)
- **Explore activity of nivo + ipi rescue, if no response to nivo/pembro**
- Sequencing with standard therapies
  - BRAF inhibitors, RT etc
- Role in other cancers
  - RCC, Lung etc
CheckMate 012: Nivolumab Plus Ipilimumab in First-line NSCLC: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Nivo 1 + Ipi 1 Q3W</th>
<th>Nivo 1 Q2W + Ipi 1 Q6W</th>
<th>Nivo 3 Q2W + Ipi 1 Q12W</th>
<th>Nivo 3 Q2W + Ipi 1 Q6W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, %</td>
<td>13</td>
<td>25</td>
<td>39</td>
<td>31</td>
</tr>
<tr>
<td>Unconfirmed PR, %</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Confirmed DCR, %</td>
<td>55</td>
<td>58</td>
<td>74</td>
<td>51</td>
</tr>
<tr>
<td>ORR in PD-L1 &gt;1% (+)</td>
<td>8</td>
<td>24</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>ORR in PD-L1 negative</td>
<td>15</td>
<td>14</td>
<td>22</td>
<td>0</td>
</tr>
</tbody>
</table>

Rizvi, et al WCLC 2015
## Anti-tumour efficacy of nivolumab-ipilimumab combination therapy (CheckMate-016)

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (n=47)</th>
<th>Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (n=47)</th>
<th>Nivolumab 3 mg/kg + ipilimumab 3 mg/kg (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed ORR, n (%) 95% CI</strong></td>
<td>18 (38.3) 24.5–53.6</td>
<td>19 (40.4) 26.4–55.7</td>
<td>0</td>
</tr>
<tr>
<td><strong>Best overall response, n (%)</strong></td>
<td>CD</td>
<td>CD</td>
<td>CD</td>
</tr>
<tr>
<td>CR</td>
<td>4 (8.5)</td>
<td>1 (2.1)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>14 (29.8)</td>
<td>18 (38.3)</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>17 (36.2)</td>
<td>17 (36.2)</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>PD</td>
<td>10 (21.3)</td>
<td>7 (14.9)</td>
<td>1 (16.7)</td>
</tr>
</tbody>
</table>

Ipilimumab ORR = 9%
Nivolumab ORR = 13-25%
Nivo/Ipi RR > Nivo RR + Ipi RR
Immune Checkpoints Regulate Strength and Type of Anti-Tumor Immune Response

Pardoll, Nat Rev Cancer 2012

Fink Z, Prop Think, Dec 2014
A Roadmap of Immunotherapy - Tumor Interactions

1. Release of cancer cell antigens
   - Chemotherapy
   - Radiation therapy
   - Targeted therapy

2. Cancer antigen presentation
   - Vaccines
   - IFN-α
   - GM-CSF
   - Anti-CD40 (agonist)
   - TLR agonists

3. Priming and activation
   - Anti-CTLA4
   - Anti-CD137 (agonist)
   - Anti-OX40 (agonist)
   - Anti-CD27 (agonist)
   - IL-2
   - IL-12

4. Trafficking of T cells to tumors

5. Infiltration of T cells into tumors
   - Anti-VEGF

6. Recognition of cancer cells by T cells
   - CAR Ts

7. Killing of cancer cells
   - Anti-PD-L1
   - Anti-PD-1
   - IDO inhibitors

Considerable research is still required to optimally apply novel immunotherapies

- Optimal treatment setting for a particular tumor
- Optimal combinations for particular tumors
- Integration with standard therapies
- Approach to patients with innately resistant (non-inflamed) tumors
- Treatment of anti-PD1 failures
- Role of the gut microbiome (toxicity and activity) and host immune polymorphisms
- Cost
updated as previous focus on PD-1 pathway was not balanced

Author, 7/20/2014