Personalized Immunotherapy for Non-small Cell Lung Cancer

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Associate Cancer Center Director for Translational Research

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Plan for this Presentation

• Immunotherapy has already been much discussed at this meeting
• Experience in Melanoma is guiding lung cancer combination therapy
• I will provide my version of the top ten lessons learned so far in NSCLC
Top Ten Lessons Learned about Immunotherapy for NSCLC

6. The PDL1 Biomarker(s) has some flaws
7. These agents, while different from chemotherapy, do have unique toxicities
8. All checkpoint antibodies are not the same? Or are they?
9. It is still unclear what is the most appropriate endpoint
10. These agents really work- it is clearly a breakthrough for patients!
Top Ten Lessons Learned about Immunotherapy for NSCLC

6. The PDL1 Biomarker(s) has some flaws
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Anti-PD-1 Therapy
Pre/Post MDX 1106 (Dec / Feb ’10)

– 66 y/o ex smoker with KRAS mutant adenocarcinoma of the lung
– 5 prior treatments for Stage IV disease
– RUQ abdominal pain, anorexia and fatigue resolved within 2 months
– Duration of response: 10 months

Courtesy of S. Gettinger
## Activity of anti-PD1 and anti-PD-L1 in NSCLC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose mg/kg</th>
<th>N=</th>
<th>ORR&lt;sup&gt;a,b&lt;/sup&gt; % (n/N)</th>
<th>Estimated Median DOR Weeks (Range)</th>
<th>PFS rate at 24 weeks</th>
<th>Median PFS Months (95% CI)</th>
<th>Median OS Months (95% CI)</th>
<th>1 yr/2yr survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>1-10 mg/kg q2w</td>
<td>129</td>
<td>17.1%</td>
<td>74.0</td>
<td>ND</td>
<td>2.3</td>
<td>9.9</td>
<td>42%/24%</td>
</tr>
<tr>
<td>MK-3475</td>
<td>2-10 mg/kg q2-3w</td>
<td>146</td>
<td>19%</td>
<td>ND</td>
<td>ND</td>
<td>Approx 2.5</td>
<td>Approx 8</td>
<td>ND</td>
</tr>
<tr>
<td>MPDL3280A</td>
<td>0.01-20 mg/kg q3w</td>
<td>53</td>
<td>23%</td>
<td>ND</td>
<td>46%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>BMS-936559</td>
<td>1-10 mg/kg q2w</td>
<td>49</td>
<td>10%</td>
<td>ND</td>
<td>31%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Medi-4736</td>
<td>0.1 -10 mg/kg q2w</td>
<td>84</td>
<td>~16%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>
CHECKMATE 063: OS in All Treated Patients

<table>
<thead>
<tr>
<th></th>
<th>Median OS, months (95% CI)</th>
<th>1-year OS rate, % (95% CI)</th>
<th>Number of events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.2 (6, 11)</td>
<td>41 (32, 50)</td>
<td>72/117</td>
</tr>
</tbody>
</table>

**Median OS = 8.2 months**

**1-year OS = 41%**

**Median follow-up for survival: 8 months (range, 0-17 months)**

Based on July 2014 DBL; Symbols represented censored observations

KEYNOTE-001: PFS, OS, and ORR by PD-L1 Expression

Analysis cutoff date: March 3, 2014.
MPDL3280A Phase Ia: Response by Smoking and Mutational Status

**Smoking Status (NSCLC; n = 53)**
- **Former / Current Smokers:** 81% (11/14), 9% (1/10)
- **Never Smokers:** 19% (2/10)

**EGFR Status (NSCLC; n = 53)**
- **EGFR WT:** 76% (9/12), 13% (1/10), **Unknown:** 11% (1/10), **EGFR Mutant:** 11% (2/18)

**KRAS Status (NSCLC; n = 53)**
- **KRAS WT:** 51% (8/16), 30% (2/6), **Unknown:** 19% (1/5), **KRAS Mutant:** 19% (1/5)

**Response by Smoking Status (ORR)a**
- **Former / Current Smokers:** 26% (11/43), 10% (1/10)
- **Never Smokers:**

**Response by EGFR Status (ORR)a**
- **EGFR WT:** 23% (9/40), 17% (1/6)
- **EGFR Mutant:**

**Response by KRAS Status (ORR)a**
- **KRAS WT:** 30% (8/27), 10% (1/10)
- **KRAS Mutant:**

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*a ORR includes investigator-assessed u/c PR by RECIST 1.1. Patients first dosed at 1-20 mg/kg by Oct 1, 2012. Data cutoff: Apr 30, 2013.*
Top Ten Lessons Learned about Immunotherapy for NSCLC

6. The PDL1 Biomarker(s) has some flaws
7. These agents, while different from chemotherapy, do have unique toxicities
8. All checkpoint antibodies are not the same? Or are they?
9. It is still unclear what is the most appropriate endpoint
10. These agents really work - it is clearly a breakthrough for patients!
Delayed Response of Metastatic NSCLC (Nivolumab, 10mg/kg)  Pseudoproggression

- Initial progression of pulmonary lesions in a patient with EGFR mutant (del19, T790M) NSCLC, followed by regression
- Prior treatment with gemcitabine/carboplatin, erlotinib, erlotinib + LBH589, and pemetrexed
Endpoints for Combinations with CTLA-4 or PD-1 pathway blockade

- ORR
- iRC RR -
- CR –
- CBR/DCR –
- **Aggregate clinical activity** -
- ‘Deep’ (> 80% regression) responses -
- Median duration of response –
- Median PFS -
- 1-year and 2 year PFS –
- 3 year PFS
- Median Survival –
- 1- year and 2-year survival
Where we are now

Where we want to be

Control
Targeted therapies
Immune checkpoint blockade
Combinations/sequencing/biomarker selection

Survival vs. Time

8. All checkpoint antibodies are not the same? Or are they?
Are there differences in Activity/Toxicity among agents

- Binding Affinity
- Different targets
- Antibody Isotype (IgG4 vs IgG1 vs engineered)
- ADCC
- Anti PD1 vs anti PD1
Programmed Death Receptor 1 (PD1)/ B7-H1 Pathway

Inflammation (e.g. IFNγ)

T cell inactivation

cytokines

PD1/ PDL1 Blockade in Clinical Trials

<table>
<thead>
<tr>
<th>Anti-PD1</th>
<th>Nivolumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>CT-011</td>
<td></td>
</tr>
<tr>
<td>AMP-514</td>
<td></td>
</tr>
<tr>
<td>AMP-224</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anti-PDL1</th>
<th>MPDL3280A</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDI4736</td>
<td></td>
</tr>
<tr>
<td>BMS-936559</td>
<td></td>
</tr>
<tr>
<td>MSB0010718C</td>
<td></td>
</tr>
</tbody>
</table>
PD1 vs. PDL1 Blockade

Tumor cell/APC

- PDL1
- PDL2
- B7.1
- Anti-PDL1
- Anti-apoptotic (tumor)

T cell

- PD1
- B7.1
- Anti-PD1

T cell inactivation
Comparison of Therapeutic Antibodies Blocking PD-L1/PD-1 Interaction

† at clinically relevant doses

Examples:

**IgG1 wt**
Anti-PD-1

ADCC intact ➔
Potential to deplete activated T cells and TILs and diminish activity

Blocks PD-1/PD-L2 interaction in lungs ➔
*Potential for autoimmune pneumonitis*

**IgG4 hinge mutant**
Anti-PD-1

40% reduced ADCC† ➔
Potential to deplete activated T cells and TILs and diminish activity

Blocks PD-1/PD-L2 interaction in lungs ➔
*Potential for autoimmune pneumonitis*

**IgG1 Engineered**
Anti-PD-L1
*MPDL3280A*

No ADCC† ➔
Decreased potential to deplete activated T cells and TILs

Leaves PD-1/PD-L2 interaction intact in lungs ➔
*Decreased potential for autoimmune pneumonitis*

Blocks PD-L1/B7.1 interaction ➔
*Potential for enhanced priming*
7. These agents, while different from chemotherapy, do have unique toxicities
<table>
<thead>
<tr>
<th>System</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>diarrhea, colitis, perforation</td>
</tr>
<tr>
<td>Renal</td>
<td>acute interstitial nephritis</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pneumonitis</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Lichenoid/ spongiotic dermatitis, rash, vitiligo</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Central and peripheral (aseptic meningitis, Guillan-Barre syndrome, myasthenia gravis,</td>
</tr>
<tr>
<td>Endocrine</td>
<td>hypophysitis, hypopituitarism, thyroiditis, adrenal insufficiency</td>
</tr>
<tr>
<td>Ocular</td>
<td>uveitis, iritis, or episcleritis.</td>
</tr>
</tbody>
</table>
Dermatitis

• Symptoms:
  – Maculopapular rash (may be pruritic)
  – Distribution on trunk, hands and feet
    • May be intense and widespread
  – Stevens-Johnson syndrome, toxic epidermal necrolysis, blistering/peeling skin; epidermal spongiosis, eosinophilic infiltrates, hair depigmentation
  – Mucositis and oral lesions

• Initial work-up:
  – Dermatology referral
  – Rule out allergic causes, contact dermatitis
Top Ten Lessons Learned about Immunotherapy for NSCLC

6. The PDL1 Biomarker(s) has some flaws
PD-L1 Immunohistochemistry (5H1): Role as a Biomarker

A. PDL1 + tumor with TILS
B. PDL1 + tumor
C. Control antibody
Assay Methodology

• Bx type - Excisional versus core versus FNA
• **Addressing heterogeneity** – multiple tumors and multiple passes within a tumor
• Interval between biopsy and treatment – effect of other therapies
• Primary versus metastatic disease
• Antibody and staining conditions
• Frozen versus FFPE tissue
• Automated versus ‘manual’ read
• **Defining a positive result (cut-offs):**
  – Cell type expressing PD-L1 (immune cell versus tumor or both)
  – Presence or absence of T-cells near PD-L1 expression
  – Location of expression – cell surface versus intracellular
  – intensity
  – Distribution - patchy versus diffuse, intratumoral versus peripheral
  – percent of cells ‘positive’
PD-L1 expression was measured in archival pretreatment tumor tissue (including >1 year old).

Responses were seen in both PD-L1+ and PD-L1− patients; ORRs were 15% (5/33) and 14% (5/35), respectively.

In the subset of patients for whom tissue was available, PD-L1 expression appeared to have no clear association with OS; median OS was 7.8 and 10.5 mo in PD-L1+ and PD-L1− patients, respectively.

PD-L1 expression was measured using the automated IHC assay based on the anti-PD-L1 monoclonal antibody (clone 28.8). Positive staining with this assay is defined as tumor cell membrane staining at any intensity, analyzed with cut-off values of 1% and 5% in a minimum number of 100 evaluable cells.
# CHECKMATE 063: Exploratory Analysis of ORR by PD-L1 Expression

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>ORR, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>15 (17/117)</td>
</tr>
<tr>
<td>PD-L1</td>
<td></td>
</tr>
<tr>
<td>≥1%</td>
<td>20 (9/45)</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>13 (4/31)</td>
</tr>
<tr>
<td>≥5%</td>
<td>24 (6/25)</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>14 (7/51)</td>
</tr>
<tr>
<td>Non-evaluable</td>
<td>30 (3/10)</td>
</tr>
</tbody>
</table>

- 86 available sample
- 76 evaluable samples

*July 2014 DBL; * One responder did not have tumor tissue available
Response Rate by Level of PD-L1 Expression
(RECIST 1.1, Central Review)

Evaluable patients were those patients in the training set with evaluable tumor PD-L1 expression who had measurable disease at baseline per imaging assessment criteria.

Analysis cut-off date: March 3, 2014.

[Bar chart showing ORR by level of PD-L1 expression:]
- Total (N=129): 22
- Strong Positive (n=41): 37
- Weak Positive (n=46): 17
- Negative (n=42): 10

*Evaluable patients were those patients in the training set with evaluable tumor PD-L1 expression who had measurable disease at baseline per imaging assessment criteria. Analysis cut-off date: March 3, 2014.*
Kaplan-Meier Estimates of Survival

PFS (RECIST v1.1, Central Review)

- PFS was longer in patients with PD-L1 strong-positive versus PD-L1 weak-positive/negative tumors (HR, 0.52; 95% CI, 0.33-0.80)
- OS was longer in patients with PD-L1 strong-positive versus PD-L1 weak-positive/negative tumors (HR, 0.59; 95% CI, 0.35-0.99)

*Evaluable patients were those patients in the training set with evaluable tumor PD-L1 expression. Strong PD-L1 positivity defined as staining in ≥50% of tumor cells, and weak PD-L1 positivity as staining in 1-49% of tumor cells. Negative staining is no PD-L1 staining in tumor cells. Data cut-off: March 3, 2014.*
MPDL-3280 Dx PD-L1 IHC Reagent – a Robust Assay to Measure PD-L1 in Human Tissues

**PD-L1 IHC (MPDL-3280 Dx):**
- Monoclonal Ab against human PD-L1
- High sensitivity and specificity
- No background
- Recognizes PD-L1 in tumor cells and tumor infiltrating immune cells

**PD-L1 expression in control cell lines**
- PD-L1 negative
- PD-L1 low
- PD-L1 medium
- PD-L1 high

**Positive tissue control**
- Placenta
# PD-L1 Status and Predictive Biomarkers in NSCLC Patients Treated With MPDL3280A: Efficacy

Elevated baseline PD-L1 expression is associated with response to MPDL3280A

<table>
<thead>
<tr>
<th>PD-L1 Status</th>
<th>N = 53</th>
<th>ORR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PD Rate&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC 3 (n = 6)</td>
<td></td>
<td>83% (5/6)</td>
<td>17% (1/6)</td>
</tr>
<tr>
<td>IHC 2 and 3 (n = 13)</td>
<td></td>
<td>46% (6/13)</td>
<td>23% (3/13)</td>
</tr>
<tr>
<td>IHC 1/2/3 (n = 26)</td>
<td></td>
<td>31% (8/26)</td>
<td>38% (10/26)</td>
</tr>
<tr>
<td>All patients &lt;sup&gt;c&lt;/sup&gt; (N = 53)</td>
<td></td>
<td>23% (12/53)</td>
<td>40% (21/53)</td>
</tr>
</tbody>
</table>

<sup>a</sup> ORR includes investigator-assessed unconfirmed and confirmed PR by RECIST v1.1.

<sup>b</sup> PD rate indicates patient with best response with progressive disease.

<sup>c</sup> Includes patients with IHC 0/1/2/3 and 7 patients with unknown diagnosis.

High MET protein, FGFR amp, mutation or fusion, PIK3CA mutation, CCND1/2, or CDK4 mutation, or no marker.

Lung-MAP Trial Arms

Patients with squamous cell lung cancer

Tumor sample analyzed

Arm A: No Marker
Arm B: PIK3CA mutation
Arm C: CCND1/2, or CDK4 mutation
Arm D: FGFR amp, mutation or fusion
Arm E: High MET protein

Treatments: CHEMO, Medi 4736, GDC 0032, Pablociclib, AZD 4547, Erlotinib, Erlotinib + Rilotumumab
Top Ten Lessons Learned about Immunotherapy for NSCLC

1. It's a Horse Race!!
2. Immunotherapy will be Used in all Lines of Therapy:
3. Combination therapy is a Must: the search for other checkpoints should continue
4. Questions remain regarding dose and duration of therapy
5. Science can help drive the Show: Biopsies and Immune monitoring should be done when possible
Correlation of Radiographic and Pathologic Response to MPDL3280A

Baseline (5-21-12)

H&E

CD8

Stroma with distorted immune cells

Extensive necrosis

Possible viable tumor cells

46 y.o. male, former smoker (20 PYH); EGFR–, ALK– and RAS–negative; PD-L1 IHC 1; 6 prior regimens
The cancer-immunity cycle

1. Release of cancer cell antigens (cancer cell death)

Recognition of cancer cells by T cells (CTLs, cancer cells)

Killing of cancer cells (immune & cancer cell)

Infiltration of T cells into tumors (CTLs, endothelial cells)

Tracking of T cells to tumors (CTLs)

Cancer antigen presentation (DC & APCs)

Priming & activation (APCs & T cells)

[Chen & Mellman Immunity 39, July 25, 2013]
MPDL3280A Leads to Increased T-cell Activation in PD-L1–Positive Patient Responding to Treatment

Possible MoA of response to MPDL3280A:
- Pre-existing intra-tumoral CD8+ T cells
- Increased trafficking or proliferation of intra-tumoral CD8+ cells
- Increased T-cell activation and cytotoxicity (e.g., Granzymes and Perforin production)
PD-L1–Negative Patient Not Responding to MPDL3280A Exhibits Low Frequency of Intratumoral T cells

Possible MoA of resistance:
- CD8+ T cells remain at the edge of the tumor (possible impaired trafficking)
- No increase in T-cell cytotoxicity
- No T-cell recognition of cancer antigens in this patient
Multiplex Cytokine Analysis

Cytokine analysis

• Multiplex cytokine analysis
• Detection of up to 100 analytes
  – Dual laser
  – Flow based
  – Sorting and detection
Tissue Profiling – in situ protein and mRNA

Tissue analysis

Quantitative Measurement of PD-L1 protein or mRNA in situ

Quantitative Multiplexed Objective TIL assay

Yale Cancer Center

Smilow Cancer Hospital at Yale-New Haven
CyTOF analysis

- Single cell data
- Deep profiling
- 34 simultaneous parameters (100 theoretically)
- Detection of 10k cells
- Liquid or solid tumors
Top Ten Lessons Learned about Immunotherapy for NSCLC

1. It's a Horse Race!!
2. Immunotherapy will be used in all lines of therapy.
3. Combination therapy is a must: the search for other checkpoints should continue.
4. Questions remain regarding dose and duration of therapy.
5. Science can help drive the show: Biopsies and immune monitoring should be done when possible.
MK-3475 PN010-06: Previously-Treated NSCLC

Stratification by:

1. ECOG status (0 vs 1)
2. Geographic region (East Asian vs. non-East Asian)

R = Randomization  PD = Progressive Disease  SFU = Survival Follow-up
Top Ten Lessons Learned about Immunotherapy for NSCLC

1. It's a Horse Race!!
2. Immunotherapy will be used in all lines of therapy.
3. Combination therapy is a must: the search for other checkpoints should continue.
4. Questions remain regarding dose and duration of therapy.
5. Science can help drive the show: biopsies and immune monitoring should be done when possible.

3. Combination therapy is a must: the search for other checkpoints should continue.
Combinations

• Chemotherapy
• Targeted Therapy
• Immune Therapy
• Other checkpoints- B7-H4
Cancer cells can evade immune attack by expressing PD-L1.

This will require some serious scientific analysis. The clinic must become the lab.

T-Cell Immune Checkpoints as Targets for Immunotherapy

Blocking CTLA-4 and PD-1

CTLA-4 Blockade (ipilimumab)

PD-1 Blockade (nivolumab)

Tumor Microenvironment

Activation (cytokines, lysis, proliferation, migration to tumor)
Rapid and Durable Changes in Target Lesions (melanoma)

A 52-year-old patient presented with extensive nodal and visceral disease. Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting. Within 4 wk, LDH normalized and symptoms resolved. At 12 wk, there was marked reduction in all areas of disease as shown.

Presented by: Jedd D. Wolchok, MD, PhD
Clinical activity: MEDI4736 + tremelimumab

- Overall response rate (ORR) and percentage for patient with best response of stable disease by PD-L1 status

<table>
<thead>
<tr>
<th>MEDI4736 + tremelimumab combination</th>
<th>All patients&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PD-L1&lt;sup&gt;+&lt;/sup&gt;</th>
<th>PD-L1&lt;sup&gt;-&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST response (ORR), % (n/N)</td>
<td>28 (5/18)</td>
<td>30 (3/10)</td>
<td>0 (0/1)</td>
</tr>
<tr>
<td>Stable disease, % (n/N)</td>
<td>28 (5/18)</td>
<td>40 (4/10)</td>
<td>100 (1/1)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Response evaluable (N) = patients with measurable disease at baseline + ≥1 on-treatment scan (includes discontinuations due to disease progression or death prior to first follow-up scan); RECIST response includes confirmed/unconfirmed CR or PR; Not all patients were assessed for PD-L1 status (defined by VENTANA assay)

- Tumour shrinkage (n=18)

- Best change in tumour size based on PD-L1 status (n=18)

Patients with baseline and ≥1 on-treatment scan
Data cut-off: August 25, 2014

Four Categories of Tumors Based on Presence of PD-L1 and TILS

Table 3. Proposed mechanisms associated with NSCLC resistance to anti-PD-1/B7-H1 therapy

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>B7-H1</th>
<th>TIL</th>
<th>Type</th>
<th>Tumor Distribution</th>
<th>Possible Resistance Mechanism(s)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>I</td>
<td>45%</td>
<td>Poor priming of general T cell responses</td>
<td>Peripheral CD4+ and CD8+ T cell responses to autologous tumor cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lack of inflammatory cell recruitment</td>
<td>Chemokine expression in biopsy or FFPE samples</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
<td>II</td>
<td>17%</td>
<td>Incomplete PD-1/B7-H1 pathway blockade and activation of alternate immune suppressive pathways</td>
<td>CD80 expression on TILs, expression of alternate suppressive pathways in TME</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>+</td>
<td>III</td>
<td>26%</td>
<td>Alternate immune suppressive pathways</td>
<td>Expression of select molecules in pathways with roles in evasion of NSCLC immunity</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>-</td>
<td>IV</td>
<td>12%</td>
<td>Intrinsic induction of B7-H1 by oncogenes</td>
<td>Expression of molecules triggering aberrant signaling events</td>
</tr>
</tbody>
</table>
The cancer-immunity cycle

1. Release of cancer cell antigens (cancer cell death)
2. Recognition of cancer cells by T cells (CTLs, cancer cells)
3. Infiltration of T cells into tumors (CTLs, endothelial cells)
4. Tracking of T cells to tumors (CTLs)
5. Priming & activation (APCs & T cells)
6. Cancer antigen presentation (DC & APCs)
7. Killing of cancer cells (immune & cancer cell)

[Chen & Mellman Immunity 39, July 25, 2013]
**Stimulatory & Inhibitory Factors**

**Priming & activation**
- CD28/B7.1, CD137/CD137L
- OX40/OX40L, CD27/CD70, HVEM, GITR, IL-2, IL-12
- CTA4/B7.1, PD-L1/PD-1
- PD-L1/B7.1, prostaglandins

**Cancer antigen presentation**
- TNF-α, IL-1, INF-α
- CD40L/CD40
- CDN, ATP
- HMGB1, TLR
- IL-10, IL-4, IL-13

**Release of cancer cell antigens**
- Immunogenic cell death
- Tolerogenic cell death

**Tracking of T cells to tumors**
- Chemokines; CX3CL1, CXCL9, CXCL10, CCL5

**Infiltration of T cells into tumors**
- LFA1/ICAM1 Selections
- VEGF, Endothelin B-R
- Hyaluronin

**Recognition of cancer cells by T cells**
- TCR
- Reduced HLA

**Killing of cancer cells**
- INF-γ T cell granule content
- PD-L1/PD-1, PD-L1/B7.1
- IDO, TGF-β, BTLA, VISTA
- LAG-3, Arginase, MICA/MICB
- B7-H4, TIM-3/phospholipids

**Blood vessel**

**Tumor**

**Lymph node**

**Tracking of T cells to tumors**
- Chemokines; CX3CL1, CXCL9, CXCL10, CCL5

**Infiltration of T cells into tumors**
- LFA1/ICAM1 Selections
- VEGF, Endothelin B-R
- Hyaluronin

**Recognition of cancer cells by T cells**
- TCR
- Reduced HLA

**Killing of cancer cells**
- INF-γ T cell granule content
- PD-L1/PD-1, PD-L1/B7.1
- IDO, TGF-β, BTLA, VISTA
- LAG-3, Arginase, MICA/MICB
- B7-H4, TIM-3/phospholipids
Top Ten Lessons Learned about Immunotherapy for NSCLC

2. Immunotherapy will be Used in all Lines of Therapy
Ongoing Phase II/III Trials for Advanced NSCLC

- Salvage Docetaxel vs. PD1/PDL1 monotherapy
  - Nivolumab. Squamous/Non-squamous trials accrual complete (no PDL1 requirement)
  - MK 3475. Ongoing (PDL1+)
  - MPDL3280A. Ongoing (PDL1+)
- Third Line
  - Nivolumab. Squamous cell (> 2 prior lines of therapy)
- First Line
  - Nivolumab vs. standard chemotherapy (PDL1+). Phase I and II studies in PDL1+ patients (chemo-naïve cohorts)
  - Accelerated approval if high RR in Phase II Setting

- Maintenance
- Adjuvant
- Neoadjuvant
- Combinations
Top Ten Lessons Learned about Immunotherapy for NSCLC

1. It’s a Horse Race!!

I predict the first checkpoint drug approved for NSCLC will be:

I don’t know

• The winning group will be the one with the best drug, best biomarker, best strategy and a little bit of luck!!!

• The winners are the patients! Thank You!!!