The Future of Immunotherapy Development: Strategies for Combination Therapy

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Melanoma is the Prototype for modern immunotherapy
“metastatic melanoma is a disease that gives cancer a bad name”(*)

(*)From the FDA Advisory Committee Report on the use of Proleukin [IL-2] for metastatic melanoma
Melanoma Disseminates Widely
Half the patients with metastatic disease die within 1 year.

70% of the patients with metastatic disease are dead by year 2.

> Half the patients with completely resected LN positive disease are dead by year 5.

Balch et al, 2001

- A study of “high quality” clinical trials

- There is a **trend** to higher response rates with more aggressive therapies.

- This does **not** correlate with a significant improvement in survival.

It doesn’t matter what you do – median survival was only **8 months** in this study.
SEVEN New Drugs over the Past 4 years reflecting new understanding of melanoma biology

- Ipilimumab 3/2011
- Peg-Interferon 3/2011
- Vemurafenib 8/2011
- Dabrafenib 5/2013
- Trametinib 5/2013
- Combination 1/9/2014
- Dabrafenib+Trametinib
- Pembrolizumab 9/04/2014
- Nivolumab 12/22/2014
Immunotherapy can cure.

Before immunotherapy

8 weeks after immunotherapy
Melanoma Case: IL-2 responses
Melanoma Case: IL-2 responses
Immunotherapy is ‘timely’.
Thursday, September 4th, 2014
Today’s Roadmap

Mechanism – Based Approach
- How does the immune system attack cancer?
- Cytokines, Checkpoint Inhibitors, Vaccines
- The Good, The Bad, and The Ugly

A Rational Approach to Combination Therapy
- Recognition, Permission, Propagation
- Non overlapping resistance
- Non overlapping toxicity ..... Maybe!

Personalized Immunotherapy
- “BIO”markers: clinical, tissue, molecules

So, what happens on Monday?
Today’s talk will not leave you sated
Today’s Roadmap

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So, what happens on Monday?
The Tissues and Organs of the Immune System

**B Cell Differentiation**
- Bone marrow
- Stem cell
- B cells

**T Cell Differentiation**
- Thymus
- T cells

**Take up residence**
- In outer cortex of lymph node
- In inner area of lymph node

**Human Body Diagram**
- Adenoids
- Tonsil
- Thoracic Duct
- Left subclavian vein
- Right Lymphatic Duct
- Thymus
- Lymph Nodes
- Spleen
- Peyer’s patches
- Large Intestine
- Small Intestine
- Bone Marrow
- Tissue Lymphatics
The Front Line: The Lymphatic System

- Afferent lymphatics
- Lymphatic valve
- Lymph node
- Deposit of metastatic melanoma
- Nodal capsule
- Germinatal center
- Medullary sinus
- Efferent lymphatic
- Artery
- Vein
- Lymphocyte

CT scan of lymph nodes.
Cells of the Immune System

- B cell
- $T_H$ cell
- $T_C$ cell
- NK cell
- Dendritic cell
- Monocyte
- Neutrophil

- Antibodies
- Cytokines
- Compliment Chemokines

Role of the Immune System in Controlling Cancer

Antibody

Malignant cell

NK cell

Macrophage

$T_H$ cell

$T_C$ cell
Dendritic Cells Sample their Surroundings
DCs actively sample the tumor environment
Dendritic Cells interact with other immune cells
T cells and DCs interact

Distinct T cell dynamics in lymph nodes during the induction of tolerance and immunity
Dendritic Cells Directly Interact with T-Lymphocytes

http://www.nature.com/ni/focus/niches/videolibrary/index.html
Activated Lymphocytes search for the target
Cytotoxic T Lymphocytes Infiltrating a Tumor during Adoptive Immunotherapy

Immune cells possess granules
Killer T cell recognizing a cancer cell
Cytotoxic T-Lymphocyte Killing Target

© James A. Sullivan
Quill Graphics
Charlottesville, VA USA
Generating an Anti-Tumor Response: Overview

Dendritic cell

TUMOR

Activated T cell

Resting T cell

T cell clonal expansion

perforin, granzyme, cytokines

T cell

MHC

B7

TCR

CD28

Tumor antigen

LYMPH NODE
Today’s Roadmap

Mechanism – Based Approach
• How does the immune system attack cancer?
• **Cytokines, Checkpoint Inhibitors, Vaccines**
• The Good, The Bad, and The Ugly

A Rational Approach to Combination Therapy
• Recognition, Permission, Propagation
• Non overlapping resistance
• Non overlapping toxicity ..... Maybe!

Personalized Immunotherapy
• “BIO” markers: clinical, tissue, molecules

So, what happens on Monday?
Currently FDA-Approved
Immunotherapy of Metastatic Melanoma

**Immunotherapy**

- Interleukin – 2
- Check point inhibitors
  - Anti-CTLA4
  - Anti-PD-1
IL-2 is in the center of the Immune Response

**Bottom Line:** IL-2 is the only approved cytokine for metastatic melanoma

Durable responses with HD IL-2

Eight Phase II clinical studies conducted at 22 institutions

The immunotherapy plateau

Currently FDA-Approved Immunotherapy of Metastatic Melanoma

Immunotherapy

Interleukin – 2

Check point inhibitors
  • Anti-CTLA4
  • Anti-PD-1
Antibodies to CTLA-4 bind to CTLA-4 on the cell surface. CTLA-4 cannot bind B7.

CTLA-4 Blockade Enhances Tumor-Specific Immune Responses

Inhibit the Inhibitor

Diagram:
- Tumor
- APC
- Antibodies to CTLA-4
- Peptide/MHC
- TCR
- CD28
- CTLA-4
- B7-1,2

Other treatments:
- Necrotic Death
- Vaccines
- Chemotherapy
- Irradiation
- Hormone therapy
- Anti-angiogenesis
- Antibodies
- "Targeted" Therapies
Autoimmune-Related Toxicity

Hypopituitarism consistent with ipilimumab-induced hypophysitis

Dilated transverse colon (arrow) with adjacent free intraperitoneal air

O’Regan, Hodi S, Radiologic Aspects of Immune-Related Tumor Response Criteria and Patterns of Immune-Related Adverse Events in Patients Undergoing Ipilimumab Therapy, AJR 2011; 197:W241–W246
Conclusions

- Ipilimumab toxicity onset is variable (3 weeks to > 3 months)
- Resolution takes on the orders of weeks to months
- Some toxicities are long term (but may not matter)
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%)

Currently FDA-Approved Immunotherapy of Metastatic Melanoma

**Immunotherapy**

Interleukin – 2

Check point inhibitors
  - Anti-CTLA4
  - **Anti-PD-1**
The Programmed Death -1 (PD-1) Pathway

Effector T cell
Immune Response

Proliferation
Cytokines (IFN-γ)
Cytotoxicity

Chronic infection
Persistent antigen stimulation

CD80, CD86
CD28
MHC
Peptide Antigen
TCR
PD-L1
PD-1
Blocking Antibody

APC or Tumor Cell

McDermott DF, Atkins MB. Cancer Medicine 2013: 2(5): 662-673
27 melanoma patients receiving anti–PD-1 antibody at a dose of 1.0 mg / kg q2weeks.

“In the majority of patients who had an objective response, responses were durable and evident by the end of cycle 2 (16 weeks)” 

65 of 306 pts had ORR (CR/PR):

- 30 of 65 (46%) responses were evident at first tumor evaluation (8 wks)
- 35 of 65 (54%) responses were ongoing at time of data analysis
- Responses persisted off drug

- 88% of responses ongoing
- Median response duration not reached (range, 6+ to 76+ weeks)


Nonsmall cell lung cancer responds to anti-PD-1 Therapy!

### Table: Response to Anti-PD-1 Therapy

<table>
<thead>
<tr>
<th>Dose of Anti–PD-1 Antibody</th>
<th>Objective Response†</th>
<th>Objective-Response Rate‡</th>
<th>Duration of Response§</th>
<th>Stable Disease ≥24 wk</th>
<th>Progression-free Survival Rate at 24 wk¶</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients/total no. of patients</td>
<td>% (95% CI)</td>
<td>mo</td>
<td>no. of patients/total no. of patients</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>All types</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0 mg/kg</td>
<td>1/18</td>
<td>6 (0.1–27)</td>
<td>9.2+</td>
<td>1/18</td>
<td>6 (0.1–27)</td>
</tr>
<tr>
<td>3.0 mg/kg</td>
<td>6/19</td>
<td>32 (13–57)</td>
<td>30.8+, 17.6+, 5.5+, 3.7+, 1.9+, NA**</td>
<td>2/19</td>
<td>11 (1–33)</td>
</tr>
<tr>
<td>10.0 mg/kg</td>
<td>7/39</td>
<td>18 (8–34)</td>
<td>14.8+, 7.6+, 7.3+, 6.7, 4.2, 3.7+</td>
<td>2/39</td>
<td>5 (0.6–17)</td>
</tr>
<tr>
<td>All doses</td>
<td>14/76</td>
<td>18 (11–29)</td>
<td>5/76</td>
<td>7 (2–15)</td>
<td>26 (16–36)</td>
</tr>
<tr>
<td>Event</td>
<td>All Events</td>
<td>Grade 3 or 4 Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>------------</td>
<td>---------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event of special interest*</td>
<td>122 (41)</td>
<td>18 (6)</td>
<td></td>
<td></td>
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<tr>
<td>Pulmonary disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>9 (3)</td>
<td>3 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>4 (1)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33 (11)</td>
<td>3 (1)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Skin events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rash</td>
<td>36 (12)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pruritus</td>
<td>28 (9)</td>
<td>1 (&lt;1)</td>
<td></td>
<td></td>
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<tr>
<td>Vitiligo</td>
<td>8 (3)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritic rash</td>
<td>6 (2)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>5 (2)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macular rash</td>
<td>4 (1)</td>
<td>1 (&lt;1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>3 (1)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>3 (1)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory investigations†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Alanine aminotransferase increased</td>
<td>11 (4)</td>
<td>2 (1)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Thyroid-stimulating hormone increased</td>
<td>9 (3)</td>
<td>1 (&lt;1)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Aspartate aminotransferase increased</td>
<td>8 (3)</td>
<td>2 (1)</td>
<td></td>
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<td></td>
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<tr>
<td>Endocrine disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>7 (2)</td>
<td>1 (&lt;1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>3 (1)</td>
<td>1 (&lt;1)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Infusion-related reaction or hypersensitivity</td>
<td>9 (3)</td>
<td>1 (&lt;1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3 deaths from drug related pneumonitis
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• Non overlapping resistance
• Non overlapping toxicity ..... Maybe!

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• “BIO”markers : clinical, tissue, molecules

So, what happens on Monday?
Does failure of one immunotherapy means that you are now resistant to all immunotherapies?
Pembrolizumab (MK-3475) in Melanoma: Response by Prior IPI and Dose/Schedule

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>CR, %</th>
<th>ORR, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPI-N</td>
<td>168</td>
<td>8</td>
<td>40 (32-48)</td>
</tr>
<tr>
<td>IPI-T</td>
<td>197</td>
<td>2</td>
<td>28 (22-35)</td>
</tr>
<tr>
<td>Total</td>
<td>365</td>
<td>5</td>
<td>34 (29-39)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>ORR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>365</td>
<td></td>
</tr>
<tr>
<td>2 mg/kg q3w</td>
<td>146</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg q3w</td>
<td>168</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg q2w</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>IPI-N</td>
<td>168</td>
<td></td>
</tr>
<tr>
<td>2 mg/kg q3w</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg q3w</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg q2w</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>IPI-T</td>
<td>197</td>
<td></td>
</tr>
<tr>
<td>2 mg/kg q3w</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg q3w</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg q2w</td>
<td>14</td>
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</table>

**Bottom Line:** No loss in efficacy in going from anti-CTLA4 ⇒ anti-PD-1

### Subgroup Analyses of Overall Survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>lpi</th>
<th>gp100</th>
<th>Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>no. of deaths/no. randomized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>100/137</td>
<td>119/136</td>
<td>0.64 (0.49–0.84)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>53/81</td>
<td>66/73</td>
<td>0.54 (0.37–0.77)</td>
</tr>
<tr>
<td>Female</td>
<td>47/56</td>
<td>53/63</td>
<td>0.81 (0.55–1.20)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>69/95</td>
<td>81/94</td>
<td>0.65 (0.47–0.90)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>31/42</td>
<td>38/42</td>
<td>0.61 (0.38–0.99)</td>
</tr>
<tr>
<td>M stage at study entry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0, M1a, M1b</td>
<td>21/37</td>
<td>31/38</td>
<td>0.47 (0.27–0.82)</td>
</tr>
<tr>
<td>M1c</td>
<td>79/100</td>
<td>88/98</td>
<td>0.72 (0.53–0.97)</td>
</tr>
<tr>
<td>Baseline LDH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ULN</td>
<td>52/84</td>
<td>66/81</td>
<td>0.56 (0.39–0.81)</td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>48/53</td>
<td>50/52</td>
<td>0.76 (0.51–1.13)</td>
</tr>
<tr>
<td>Prior use of interleukin-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19/32</td>
<td>25/33</td>
<td>0.50 (0.28–0.91)</td>
</tr>
<tr>
<td>No</td>
<td>81/105</td>
<td>94/103</td>
<td>0.69 (0.51–0.93)</td>
</tr>
</tbody>
</table>

**Bottom Line:** No loss in efficacy in going from IL-2 ⇒ ipilimumab

Enhancing the anti-tumor response

Increased antigen presentation

TUMOR

Tumor antigen

Dendritic cell

perforin
granzyme

cytokines

Activated T cell

T cell clonal expansion

Resting T cell

MHC

B7

TCR

CD28

LYMPH NODE
T-VEC: An HSV-1-Derived Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects

**Local Effect:**
Virally-Induced Tumor Cell Lysis

- Selective viral replication in tumor tissue
- Talimogene laherparepvec
- Cancer cells rupture
- Healthy cells
- GM-CSF

**Systemic Effect:**
Tumor-Specific Immune Response

- Systemic tumor-specific immune response
- CD4+ T cell (helper T cell)
- CD8+ T cell (cytotoxic T cell)
- Tumor-specific antigens
- Dying cancer cell
- Death of distant cancer cells

Slide courtesy of Dr. Igor Puzanov, with permission
There were 6 measurable lesions at baseline including 1 cutaneous neck lesion, 2 subcutaneous abdominal wall lesions (1 of which is shown), 2 intra-abdominal lesions (which are shown), and 1 in musculature of right thigh (which completely resolved). Both Injected lesions are indicated by a green arrow.
Enhancing the anti-tumor response
Checkpoint blockade + Increased antigen presentation

TUMOR

Tumor antigen
perforin
granzyme

Activated T cell

T cell clonal expansion

Resting T cell

ipilimumab

Dendritic cell

TCR
CD28

MHC
B7

perforin
cytokines

lymph node
Enhancing the anti-tumor response

Cellular approach

- TUMOR
- Activated T cell
- Resting T cell
- T cell clonal expansion
- Tumor antigen
- Dendritic cell
- MHC
- B7
- perforin
- granzyme
- cytokines
ADOPTIVE IMMUNOTHERAPY

TIL HARVEST, EXPANSION AND TIL THERAPY

Tumor removed by surgery

Lymphodepletion prior to TIL transfer (day -7)

Cy + Flu

TBI TIL

High-dose IL-2

TIL infusion

Expanded TIL (10-150 billion) pooled into one infusion bag

Rapid expansion of TIL (“REP”) (2 weeks)

Anti-CD3 Feeders IL-2

Testing Selection

TIL rapidly expanded in flasks and then in larger culture bags

Initial TIL expansion or “Pre-REP” phase (3-5 weeks)

Fragments put into culture plates

Tumor cut into small fragments

Genetic Manipulation

Whole Tumor Antigen Dendritic Cell Vaccine Study

1. Debulking
2. Tumor cells
   - HOCL Lysate
3. Debulking
4. Apheresis
5. Monos
   - GM-CSF + IL-4
6. GM-CSF + IL-4
7. Immature DC
8. LPS + IFN-γ
9. DC Vaccinations
10. Pulsing with Whole Tumor Antigen
Enhancing the anti-tumor response

Checkpoint blockade + Increased antigen presentation

TUMOR

Activated T cell

perforin

granzyme

cytokines

ipilimumab

T cell clonal expansion

Resting T cell

MHC

B7

Dendritic cell

LYMPH NODE

TCR

CD28
**Targeted Rx + Immunotherapy**

- Inhibitors possess high response rates but low cure rates (if any)
- Immunotherapy can cure but have low response rates

† 100 Melanoma Differentiation Antigen
† Lymphocyte recognition within tumor
† Biopsy Study – Increased T4 infiltration of BRAF\textsuperscript{i} tissues.

**Vemurafenib + Ipilimumab = Liver Toxicity**

### Table 1. Data for Patients with Grade 3 Elevations in Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) Levels While Receiving Combination Therapy with Vemurafenib and Ipilimumab. *

<table>
<thead>
<tr>
<th>Study Cohort and Patient No.</th>
<th>No. of Doses of Ipilimumab before ALT–AST Elevation</th>
<th>Time to Onset of ALT–AST Elevation after First Dose of Ipilimumab</th>
<th>Treatment</th>
<th>Time to Resolution of ALT–AST Elevation</th>
<th>Toxicity Relapse with Repeated Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>21 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 5 days and then restarted with dose reduction; ipilimumab permanently discontinued</td>
<td>4 days</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>36 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (2 doses)</td>
<td>6 days</td>
<td>No</td>
</tr>
<tr>
<td>6†</td>
<td>1</td>
<td>21 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 5 days and then restarted with dose reduction; ipilimumab continued (1 dose)</td>
<td>6 days</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>19 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (1 dose)</td>
<td>12 days</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Second cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>15 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 7 days and then restarted with dose reduction; ipilimumab permanently discontinued</td>
<td>10 days</td>
<td>NA</td>
</tr>
<tr>
<td>16‡</td>
<td>1</td>
<td>13 days</td>
<td>Vemurafenib and ipilimumab permanently discontinued</td>
<td>20 days</td>
<td>NA</td>
</tr>
</tbody>
</table>

Hodi FS et al. Hepatotoxicity with Combination of Vemurafenib and Ipilimumab, NEJM 368;14, 2013
“The results of this phase 1 study highlight the risk of concurrent administration of vemurafenib and ipilimumab. Our findings reinforce the need for carefully conducted trials of new combination therapies, even when both agents have regulatory approval and have distinct mechanisms of action. “
Enhancing the anti-tumor response

Dual Checkpoint blockade
Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

• 142 treatment naïve patients. 2:1 randomization to receive ipilimumab (3 mg/kg) + Nivolumab (1 mg/kg) or placebo, every 3 weeks X 4 doses.

• Followed by Nivolumab 3 mg/kg or placebo every 2 weeks.

• BRAF WT tumors: (combo vs placebo)
  • RR: 61% vs 11% (P < 0.001)
  • CR: 22% vs 0

• Toxicity: Grade III or IV in 54% vs 24%
Ipilimumab + Nivolumab or Placebo

Nivolumab plus Ipilimumab
Median Change: Decrease of 68.1%

Ipilimumab
Median Change: Increase of 5.5%

* Patient with confirmed response

Published April 20, 2015 at NEJM.org
Ipilimumab + Nivolumumab or Placebo

Death or Disease Progression

<table>
<thead>
<tr>
<th>Proportion</th>
<th>No. of Patients/Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab + Ipilimumab</td>
<td>30/72</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>25/37</td>
</tr>
</tbody>
</table>

Median Progression-free Survival

<table>
<thead>
<tr>
<th>Proportion</th>
<th>Mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab + Ipilimumab</td>
<td>NR</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>4.4 (2.8–5.7)</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.40 (95% CI, 0.23–0.68) P<0.001

Published April 20, 2015 at NEJM.org
<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab plus Ipilimumab (N=94)</th>
<th>Ipilimumab (N=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Any treatment-related adverse event</td>
<td>86 (91)</td>
<td>51 (54)</td>
</tr>
<tr>
<td>Most common treatment-related adverse events†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea‡</td>
<td>42 (45)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Rash</td>
<td>39 (41)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37 (39)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>33 (35)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Colitis‡</td>
<td>22 (23)</td>
<td>16 (17)</td>
</tr>
<tr>
<td>Nausea</td>
<td>21 (22)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Elevated alanine aminotransferase</td>
<td>21 (22)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Elevated aspartate aminotransferase</td>
<td>20 (21)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19 (20)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>15 (16)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15 (16)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (14)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 (14)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>12 (13)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>11 (12)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Pneumonitis‡</td>
<td>10 (11)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>10 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>10 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (11)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>9 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9 (10)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Astenia</td>
<td>8 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritic rash</td>
<td>3 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related adverse event leading to discontinuation of treatment</td>
<td>44 (47)</td>
<td>36 (38)</td>
</tr>
</tbody>
</table>
Today’s Roadmap

Mechanism – Based Approach

- How does the immune system attack cancer?
- Cytokines, Checkpoint Inhibitors, Vaccines
- The Good, The Bad, and The Ugly

A Rational Approach to Combination Therapy

- Recognition, Permission, Propagation
- Non overlapping resistance
- Non overlapping toxicity ..... Maybe!

Personalized Immunotherapy

- “BIO”markers: clinical, tissue, molecules

So, what happens on Monday?
Vitiligo: Hypopigmentation
OS Appears to Favor PD-L1+ Tumors Treated With Pembrolizumab*

*Based on tumor PD-L1 expression by IHC

PD-L1 negativity an unreliable biomarker

<table>
<thead>
<tr>
<th>Rx Antibody</th>
<th>Tumor type</th>
<th>N</th>
<th>PD-L1 + RR, n/N (%)</th>
<th>PD-L1 - RR, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab[1]</td>
<td>Solid tumors</td>
<td>42</td>
<td>9/25 (36)</td>
<td>0/17 (0)</td>
</tr>
<tr>
<td>Nivolumab[2]</td>
<td>Solid tumors</td>
<td>38</td>
<td>7/16 (44)</td>
<td>3/18 (17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9/23 (39)</td>
<td>5/21 (24)</td>
</tr>
<tr>
<td>Pembrolizumab[5]</td>
<td>Melanoma</td>
<td>125</td>
<td>41/83 (49)</td>
<td>4/30 (13)</td>
</tr>
<tr>
<td>Ipi/Nivo[7]</td>
<td>Melanoma</td>
<td>56</td>
<td>8/14 (57)</td>
<td>17/42 (40)</td>
</tr>
</tbody>
</table>

Improved OS with Nivo vs Dacarbazine

Regardless of PD-L1 status

Today’s Roadmap

Mechanism – Based Approach
• How does the immune system attack cancer?
• Cytokines, Checkpoint Inhibitors, Vaccines
• The Good, The Bad, and The Ugly

A Rational Approach to Combination Therapy
• Recognition, Permission, Propagation
• Non overlapping resistance
• Non overlapping toxicity ..... Maybe!

Personalized Immunotherapy
• “BIO”markers : clinical, tissue, molecules

So, what happens on Monday?
Tumor Shrinkage
Immunoresponses: tumors may get worse before getting better.
Heterogeneity of tumor response to immunotherapy
27 melanoma patients receiving anti–PD-1 antibody at a dose of 1.0 mg / kg q2weeks.

“In the majority of patients who had an objective response, responses were durable and evident by the end of cycle 2 (16 weeks)”
Immunotherapy is not about response rates, it is about the long term survival in a small subset of patients.
Where do we want to be?

![Graph showing survival rates with different treatments.](image-url)

© 2013 American Association for Cancer Research

CCR Focus

The treatment landscape
Outpatient vs. Inpatient
Acute vs. Chronic

Immune related toxicities can be moderate, severe, or life-threatening. Multiple organ systems. May be slow onset, insidious, and mimic disease progression. May mimic common ailments (diarrhea).

Major life threatening issue is capillary leak syndrome (CLS) and its downstream effects. Occurs and resolves within hours of an IL-2 dose. Patients are usually discharged free of permanent sequelae of CLS.

CTLA-4, PD-1, IL-2
Timing of Toxicity may Limit Options

- ipilimumab
- Steroid taper
- IL-2

Toxicity Grade

0  2  4  6  8  10  12  14  16  18  20  22  24  26  28  30

0  2  4  6  8  10  12  14  16  18  20  22  24  26  28  30
Regulation of T Cell Responses Via Multiple Co-Stimulatory and Inhibitory Interactions

- Targeting CTLA-4 and PD-1 inhibitory receptors has been a major clinical focus

- T cell response to antigen is mediated by peptide-MHCs recognized by TCR (first signal – specificity)

- B7 family of membrane-bound ligands binds both co-stimulatory and inhibitory receptors (second co-stimulatory signal)

Immunological “sensitive” cancers

Melanoma, Renal Cell Carcinoma, Lung, (pancreas, ovarian, Head+Neck, hematologic…)

• Possess unique antigens
  – Mutations, translocations,
  – Glycoproteins
  – Embryonic antigens exposed
  – Viral antigens (Cervical, Merkel etc)

• But…. Does it matter?
  – Can you fashion a response to any tumor?
THE BEGINNING OF THE BEGINNING
The Future of Immunotherapy Development: Strategies for Combination Therapy

Michael K Wong MD PhD
Professor of Medicine
Adams Chair in Cancer Research
Head: Solid Tumors Section

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University of Southern California
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