Advances in the Treatment of Melanoma

Medicine Conference
IU Arnett Hospital
September 24, 2014

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Assistant Professor of Clinical Medicine and Dermatology
Disclosures

- Advisory Board: Roche-Genentech, BMS
- Research Funding: Roche-Genentech, Sanofi-Aventis, Merck
- Honoraria: Dava Oncology
- Committee Co-chair: Via Oncology Pathways

• Off-label use: Temozolomide, cisplatin, carboplatin, paclitaxel, infliximab
Objectives/Topics for discussion

Melanoma Basics

Surgeon General Call to Action

Who should see a dermatologist?

Developments in the treatment of advanced melanoma

– Molecularly Targeted Therapies
  • BRAF inhibitors: Vemurafenib and Dabrafenib
  • MEK inhibitors: Trametinib
  • Common Toxicities

– Immune Checkpoint inhibitors and other immunotherapies
  – CTLA-4 antibody: Ipilimumab
  – PD-1 inhibitors: Nivolumab and Pembrolizumab
  • Management of immune related toxicities
Questions

1. Clinical Trials are a first line treatment option for advanced, unresectable melanoma. True or False?

2. What is a relative contraindication to treatment with ipilimumab?
   A. Baseline renal dysfunction from hypertension (Cr 1.5)
   B. Rheumatoid Arthritis
   C. Recent Radiation
   D. None of the above
Questions?

• 3. Patients who did not respond to ipilimumab will not respond to another immunotherapy? True or False?

• 4. Chemotherapy has no role in the treatment of advanced, unresectable melanoma? True or False?
Cutaneous Melanoma

- 76,100 estimated new cases (2014)
- 9,710 estimated deaths (2014)

- Melanoma in situ
  - Estimated new cases (2014): 63,770

- Estimated lifetime risk among Caucasian Americans:
  Male: 1 in 34  
  Female: 1 in 53
Cutaneous Melanoma

- Majority cured with surgical resection
- Tumors < 1mm have ≤ 6% risk of nodal metastases
- 5 year survival
  - Melanomas ≤1mm: 93-97%
  - Nodal involvement: 39-70%
- Metastatic - Currently rising!
- 5% of all skin cancers
- 75% of skin cancer deaths

JCO, Balch et al, 2001 and 2009

Currently rising!
Melanoma Incidence-US

Figure 3. Age-Adjusted Melanoma Incidence Rates, Actual and Projected, by Sex, 1975–2020

Note: Data after vertical dotted line are projected rates.
DeSantis, 2014, Ca Cancer J Clin

Figure EPY7: Average-years of life lost in the U.S. due to cancer, All Races, Both Sexes; 2008

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Years in thousands (1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood Ages (0-14)</td>
<td>71</td>
</tr>
<tr>
<td>Testis</td>
<td>26</td>
</tr>
<tr>
<td>Cervix Uteri</td>
<td>23</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>22</td>
</tr>
<tr>
<td>Brain &amp; ONS</td>
<td>19</td>
</tr>
<tr>
<td>Breast (Female)</td>
<td>18</td>
</tr>
<tr>
<td>Melanoma of the Skin</td>
<td>18</td>
</tr>
<tr>
<td>Ovary</td>
<td>17</td>
</tr>
<tr>
<td>Oral Cavity &amp; Pharynx</td>
<td>17</td>
</tr>
<tr>
<td>Liver &amp; IBD</td>
<td>17</td>
</tr>
<tr>
<td>Corpus &amp; Uterus, NOS</td>
<td>17</td>
</tr>
<tr>
<td>Leukemia</td>
<td>16</td>
</tr>
<tr>
<td>Esophagus</td>
<td>16</td>
</tr>
<tr>
<td>Stomach</td>
<td>16</td>
</tr>
<tr>
<td>Kidney &amp; Renal Pelvis</td>
<td>15</td>
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<tr>
<td>All Sites Combined</td>
<td>15</td>
</tr>
<tr>
<td>Lung &amp; Bronchus</td>
<td>15</td>
</tr>
<tr>
<td>Pancreas</td>
<td>15</td>
</tr>
<tr>
<td>Colon &amp; Rectum</td>
<td>15</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>14</td>
</tr>
<tr>
<td>Myeloma</td>
<td>14</td>
</tr>
<tr>
<td>Urinary Bladder</td>
<td>11</td>
</tr>
<tr>
<td>Prostate</td>
<td>0</td>
</tr>
</tbody>
</table>

July 29, 2014: Surgeon General

A Call to Action

• 1: Increase opportunities for sun protection in outdoor settings

• 2: Provide individuals with the information they need to make informed, healthy choices about UV exposure

• 3: Promote policies that advance the national goal of preventing skin cancer

• 4: Reduce harms from indoor tanning

• 5: Strengthen research, surveillance, monitoring, and evaluation related to skin cancer prevention

Recommendations

• US Preventative Services Task Force:
  • Counseling pts with fair skin age 10-24 to minimize UV exposure to reduce risk of skin cancer

• Interventions:
  • Avoid indoor tanning
  • Sun protection and sun avoidance
    • Sunscreen, sun protective clothing (hat and sunglasses)
    • Minimize time outside between 10-4pm
  • Self and physician skin monitoring for new or changing lesions
Indoor Tanning Devices

- Variable, can emit UVA and UVB
- 2009-WHO classified indoor tanning devices as Class I human carcinogen due to increased risk of BCC, SCC and melanoma
- Risk increases with younger age and frequency of use
- Meta-analysis, international, 31 studies
  - 16% increased risk of melanoma for ‘Ever’ vs ‘Never’ user of tanning bed [Colantonio, JAAD, 2014]
- US case controlled study in Minnesota: [Lazovich, Cancer Epidemiol Biomarkers Prev. 2010]
  - ‘Ever’ vs ‘Never’ user of indoor tanning before age 18 → 85% increased risk of melanoma
  - ‘Ever’ vs ‘Never’ user aged 18–24 years → increased risk by 91%
- CDC 2010 National Health Interview Survey: [CDC MMWR, 2012]
  - Non-Hispanic white women that tan:
    - Age 18-21: 32%
    - Age 22-25: 30%
- Legislation: Since October 2011, several states have enacted age limitations or parental consent
- May 29, 2014: FDA reclassified indoor tanning devices as Class II (moderate to high risk)
  - Will require a visible black box warning that people under 18 should not use as well as premarket review and performance test requirements
Indiana Tanning Laws

• IC 25-8-15.4:
  – No age ban
  – Age <16 must be accompanied by a parent/guardian
  – Age <18 must have parent/guardian written permission

• Facility:
  • Must limit time to maximum per manufacturer
  • Provide protective eyewear
  • Must have a license to operate a facility and charge a fee
  • Patrons must sign a written statement re: risk
Who should see a dermatologist?

• Any patient with a new or changing mole that is concerning
  – ‘Normal’ moles should not bleed, itch or be painful

• Patient with a history of melanoma:
  – Should be followed by a dermatologist for life
  – Risk of melanoma recurrence is lifelong
  – At risk for developing second (or third) primary melanomas

• Patients with a family history of melanoma
  – All first degree relatives should be screened annually

• Immunosuppressed patients
  – Higher risk of all skin cancers
Melanoma: Initial Assessment

- **Concerning Skin lesions**
  - ABCDEs
  - Ugly duckling
  - New lesion
    - Most stop making new nevi in 40s

- Melanomas can be skin colored (amelanotic)

- Early melanoma—more subtle in appearance

- **Risk Factors:**
  - Nevi
    - Number
    - Dysplastic
  - Personal history
  - Family history
  - Familial Melanoma Syndromes (10%)
    - 9p21 mutations (CDKN2A or p16INK4a)
    - 12q14 mutation (CDK4)
  - BRCA2
  - Skin type/sun sensitivity
  - Ethnic background
  - Sun exposure
  - Blistering burn early in life
  - Tanning bed use
  - PUVA therapy
  - Immunosuppression
    - HIV/AIDS
    - Post organ transplant
    - Immunosuppressive meds
  - Arsenic
  - Xeroderma Pigmentosum
**A** symmetry: not a mirror image

**B** order: irregular or jagged edges

**C** color: variegated. Black, brown, blue, red, white

**D**iameter: greater than 6mm (pencil eraser), or change in size

**E**volution: change in appearance or behavior (itch/bleed/pain)
Skin Biopsy

- Excisional
- Incisional
- Punch
- Shave (deep saucerization)

- Full skin thickness bx for accurate assessment of tumor thickness

- If a partial biopsy, should be from the ‘worst’ part of the lesion

- Avoid excessive margins
  - Possible disruption of lymphatics, if need for SLN

- NEVER treat with currettage, cautery or cryotherapy

- If you do not get an (appropriate) answer, do another biopsy!
The Pathology Report

- Primary vs metastasis
  - Epidermal component?
- Thickness (mm)
- Margins – extends to deep?  
  - true thickness may be greater
- Ulceration
- Mitoses (per mm2)
- Anatomic location
- LVI/PNI
- Microsatellites
- Histologic subtype
- Level of invasion
Surgical Treatment

• Wide local excision (WLE) of primary
• Recommended margins:

<table>
<thead>
<tr>
<th>Thickness</th>
<th>Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>in situ</td>
<td>0.5 cm</td>
</tr>
<tr>
<td>≤1 mm</td>
<td>1 cm</td>
</tr>
<tr>
<td>1.01-2 mm</td>
<td>1-2 cm</td>
</tr>
<tr>
<td>2.01-4 mm</td>
<td>2 cm</td>
</tr>
<tr>
<td>&gt;4 mm</td>
<td>2 cm</td>
</tr>
</tbody>
</table>

• May be modified according to feasibility: anatomic site, cosmetic outcome
  – Typically attempt 1cm margins

• For resection of metastatic foci, no guidelines other than negative margins
AJCC Staging-2010

Table 1. TNM Staging Categories for Cutaneous Melanoma

<table>
<thead>
<tr>
<th>Classification</th>
<th>Thickness (mm)</th>
<th>Ulceration Status/Mitoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1s</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
| T1             | ≤ 1.00         | a: Without ulceration and mitosis < 1/mm²  
                     b: With ulceration or mitoses ≥ 1/mm²        |
| T2             | 1.01-2.00      | a: Without ulceration       |
| T3             | 2.01-4.00      | a: Without ulceration       |
| T4             | > 4.00         | a: Without ulceration       |

<table>
<thead>
<tr>
<th>N</th>
<th>No. of Metastatic Nodes</th>
<th>Nodal Metastatic Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>N1</td>
<td>1</td>
<td>Micrometastasis*</td>
</tr>
<tr>
<td>N2</td>
<td>2-3</td>
<td>Micrometastasis*</td>
</tr>
<tr>
<td>N3</td>
<td>4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M</th>
<th>Site</th>
<th>Serum LDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
<td>NA</td>
</tr>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous, or nodal metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

Table 2. AJCC Anatomic Staging for Melanoma

<table>
<thead>
<tr>
<th>Staging</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IB</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIB</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIC</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Melanoma: Classification

• Primary Site
  – Cutaneous (>90%)
  – Mucosal (~2%)
  – Ocular/Uveal (~3-4%)

• Majority seen in Medical Oncology are advanced, unresectable or stage II or III

• Many will be on clinical trials

• **Things to know:**
  • Primary features
    – Thickness (mm)
    – Ulceration
    – Mitoses
  
  • Has it been widely excised?

  • Lymph nodes involved?
    – SLN versus palpable?
    – How many?

  • Distant Metastases?
    – Where?
    – What is there current tx?
Adjuvant options for Stage IIB/C or III

1. Close Observation
   - Med/surg Onc and Derm
   - q3-mo x 1-2 yrs, then q4-6mo until year 5, then qyr (NCCN guidelines)
     - Derm f/u for life
     - Eval for recurrence as well as new primaries

2. Interferon alfa-2b
   - T>4mm, or LN+ (IIB, IIC, III)
   - Limited data with in transit dz. No data in resected stage IV (ECOG 1609 ongoing)

3. Pegylated Interferon alfa
   - FDA approved in 3/2011
   - Stage III – LN involvement only

4. Clinical Trials
   - Vaccines
     - Peptide (majority, HLA A2+)
     - Autologous (few)
   - Variations on IFN
   - Gene modified T cells
   - Ipilimumab:
     - EORTC18071 – ipi 10mg/kg x 3 yrs vs placebo - awaiting results
     - ECOG 1609: RCT phase III – HD IFN vs ipilimumab (resected stage IIIB-IVM1b)
   - Targeted therapy: randomized, double-blind phase III studies:
     - Vemurafenib x 52 weeks vs placebo
     - Dabrafenib + Trametinib x 52 weeks vs placebos
Melanomas – Take Home Points

• Negative margins on 1º melanoma biopsy never adequate – Need wide local excision (2nd procedure)

• Verify adequate clinical margins in operative note

• WLE may performed by: dermatologic surgeons, plastic surgeons, ob-gyn, colorectal surgeons, ENT, surgical oncologists

• SLN preferably performed at time of WLE
  • Requires expertise

• CLND is current standard of care for ANY LN involvement

• At a minimum, any melanoma patient needs annual derm exam for life
Advanced Melanoma: A Changing Landscape

- Ipilimumab - first systemic therapy to impact OS
- MAPK targeted inhibitors have dramatic activity and improve OS
- PD-1 inhibitors evidencing a rapid onset of action and durable benefit with impressive survival
- Combination therapy within and across modalities, as well as sequencing of agents, is being defined and optimized
- Subclassification according to molecular and genetic aberrations continues to evolve
- Identification and validation of prognostic and predictive biomarkers is essential

Overall survival for metastatic melanoma is rising
Melanoma Timeline – FDA approved agents

• **Resected melanoma:**
  - 1995 – High Dose Interferon - resected stage IIB-C/III
  - 2011 - Pegylated interferon-alfa - resected stage III

**Other Agents on the Horizon**
- Nivolumab

• **Advanced, unresectable (stage III/IV) Melanoma**
  - 1975 – Dacarbazine
  - 1998 - High Dose Interleukin-2
  - 2011 – Ipilimumab
  - 2011 – Vemurafenib
  - 2013 – Trametinib
  - 2014 – Dabrafenib + Trametinib
  - 2014 - Pembrolizmab
Metastatic Melanoma: Treatments

**Local:**
- **Surgery**
  - Metastatectomy for oligometastatic disease
- **Isolated Limb Infusion or Perfusion**
  - Hyperthermic Melphalan
- **Radiation**
  - SRS/WBI
    - Brain metastases
  - Palliative
    - Brain, bone, etc.

**Systemic:**
- **Molecularly Targeted:**
  - MAPK inhibitors
    - BRAF:
      - Vemurafenib
      - Dabrafenib
    - MEK:
      - Trametinib
- **Immune/Biologics:**
  - Cytokine:
    - HD Interleukin-2
  - Checkpoint Blockade
    - Ipilimumab (CTLA-4 Ab)
    - Pembrolizumab (PD-1 Ab)
- **Chemotherapy**
  - Dacarbazine
  - Temozolomide
  - Carboplatin/paclitaxel
  - Combination therapies
  - Biochemotherapy
Immunotherapy

Goal: Induction of long-lasting immune response against tumor

Methods:

• Cytokines: IFN, High dose IL-2, GM-CSF
• Vaccines
• Adoptive cell transfer
• Checkpoint inhibitors
  – Ipilimumab
  – Nivolumab
  – Pembrolizumab
Immune-modulating Therapy: Anti-CTLA-4 Antibodies

- Ipilimumab (MDX-010) and Tremelimumab (CP-675,206)
  - Fully human, monoclonal antibodies

- Extensive phase II trials –
  - Durable, prolonged stable disease rate 20-30%

- **Side effects:**
  - Infusion reactions
  - Immune-related adverse events (irAEs) – typically in first 12 weeks
    - Colitis -- DIARRHEA (30-40%; severe 5%)
    - Dermatitis (35%, severe 1%)
    - Endocrine dysfunction (5-15%)
    - Hepatitis (severe <5%)
    - Uveitis (~1%)
    - Neuropathies
    - Other immune-related adverse events possible

- Recognize early and treat aggressively
- Most respond to steroids and drug holding

- Autoimmunity can correlate with clinical response, but is not required
Phase III randomized, double-blinded trial in previously treated, unresectable stage III/IV Melanoma

- Ipilimumab + gp100 vaccine vs.
- Ipilimumab + placebo vs.
- gp100 vaccine + placebo

- Dose: 3mg/kg
- 3:1:1 randomization

Eligibility:
- HLA-A*0201
- Skin or mucosal
- At least 1 prior tx
- No autoimmune dz (except vitiligo)

Hodi et al, NEJM, 2010

1° endpoint:
- Original: BORR
- Changed to OS before unblinding: combination vs gp100

2° endpoints:
- All other OS comparisons
- BORR
- Disease control rate (DCR) to W24
- PFS
- Safety
Ipi + gp100:
- med OS = 10.0 mo
  (95% CI, 8.5 - 11.5);
- median f/u = 21.0 mo

IPI alone:
- med OS = 10.1 mo
  (95% CI, 8.0 to 13.8)
- median f/u = 27.8 mo

gp100-alone
- med OS = 6.4 mo
  (95% CI, 5.5 to 8.7)
- median f/u = 17.2 mo

Hodi et al, NEJM, 2010
Randomized Phase III: DTIC/ipi vs. DTIC/placebo in treatment naïve pts with advanced melanoma

- DTIC alone: 9.1mo
- Ipi + DTIC: 11.2 mo
- RR:
  - DTIC/placebo=10.3%
  - DTIC/placebo =15.2%

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>DTIC + IPI: Total</th>
<th>Gr3</th>
<th>Gr4</th>
<th>DTIC: Total</th>
<th>Gr3</th>
<th>Gr4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in alanine aminotransferase</td>
<td>72 (29.1)</td>
<td>37 (15.0)</td>
<td>14 (5.7)</td>
<td>11 (4.4)</td>
<td>2 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Increase in aspartate aminotransferase</td>
<td>66 (26.7)</td>
<td>34 (13.8)</td>
<td>9 (3.6)</td>
<td>8 (3.2)</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>4 (1.6)</td>
<td>3 (1.2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Robert et al, NEJM, 2011
ECCO 2013: abst 24: Pooled analysis of long term survival for ipi

- Pooled pt data across 12 prospective and retrospective phase II and III studies
  - N=1861:
    - previously treated (n=1257)
    - naïve (n=604)
  - Included 3mg/kg and 10mg/kg,
  - Most had retreatment or maintenance tx

- Med OS = 11.4 mo
  - Tx-naïve: 13.5 mo
  - Prior tx: 10.7mo

- 3yr OS rate = 22%
- 7yr OS rate = 17%, no deaths after 7 yrs

- With 2985 pts from expanded access program included, med OS 9.5mo

Schadendorf et al, ECCO 2013
Checkpoint inhibitors

Ribas, NEJM, 2012
PD-1 antibody: Nivolumab (BMS-936558, MDX-1106)

Fully human IgG4 Ab

- Phase I Study
- Advanced melanoma, RCC, NSCLC, CRC, or CRPC with PD
- Dose: q2wk x 4 doses, with additional tx if benefit

N=296; melanoma n=107

<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>0.1 mg/kg</td>
<td>4/14</td>
<td>29 (8–58)</td>
<td>7.5+, 5.6+, 5.6, 5.6</td>
<td>1/14</td>
<td>7 (0.2–34)</td>
</tr>
<tr>
<td>0.3 mg/kg</td>
<td>3/16</td>
<td>19 (4–46)</td>
<td>3.8+, 2.1+, 1.9+</td>
<td>1/16</td>
<td>6 (0.2–30)</td>
</tr>
<tr>
<td>1.0 mg/kg</td>
<td>8/27</td>
<td>30 (14–50)</td>
<td>24.9+, 22.9, 20.3+, 19.3+, 18.4+, 7.6+, 5.6+, 5.3+</td>
<td>3/27</td>
<td>11 (2–29)</td>
</tr>
<tr>
<td>3.0 mg/kg</td>
<td>7/17</td>
<td>41 (18–67)</td>
<td>22.4+, 18.3+, 15.2+, 12.9, 11.1, 9.3, 9.2+</td>
<td>1/17</td>
<td>6 (0.1–29)</td>
</tr>
<tr>
<td>10.0 mg/kg</td>
<td>4/20</td>
<td>20 (6–44)</td>
<td>24.6+, 23.9+, 18.0+, 17.0</td>
<td>0/20</td>
<td>0</td>
</tr>
<tr>
<td>All doses</td>
<td>26/94</td>
<td>28 (19–38)</td>
<td></td>
<td>6/94</td>
<td>6 (2–13)</td>
</tr>
</tbody>
</table>

Topalian et al, NEJM, 2012
Nivolumab

Topalian et al, NEJM, 2012
ASCO 2014: long term f/u - phase I nivolumab (Hodi)

- RR 32% (34/107) (all doses)
  - RP2D: 3mg/kg: RR = 41% (7/17)

- Med duration of resp = 22.9 mo

- Median OS =20.3 mo at 3mg/kg

- 1yr OS = 63%
- 2 yr OS = 48%
- 3 yr OS = 41%

- 44% (15/34) of pts with CR/PR showed response at 8 wks

- At data cutoff, 56% (19/34) of responding pts continue to respond

Presented by F.S Hodi, ASCO, 2014
411 Patients in Melanoma Expansion Cohorts: KEYNOTE-001

Presented by Antoni Ribas at 2014 ASCO Annual Meeting

Pembrolizumab

Randomized cohorts (N = 276)

- IPI Naïve 10 mg/kg Q2W (n = 41)
- IPI Treated 10 mg/kg Q2W (n = 32)
- IPI Naïve 2 mg/kg Q3W (n = 22)

Nonrandomized cohorts (N = 135)

- IPI Refractory 10 vs 2 mg/kg Q3W (n = 173)
- IPI Naïve 10 vs 2 mg/kg Q3W (n = 103)

Role of PD-L1 Abstract 3005: R. Keppord, Tues, June 3 11:09 am in S100a

irRC vs RECIST Abstract 3006: F.S. Hodi, Tues, June 3 11:21 am in S100a

Prior IPI and Dose Abstract 3000: O. Hamid, Tues, June 3 9:45 am in S100a

Presented at: ASCO 50th Annual Meeting Science & Society
Maximum Percent Change from Baseline in Tumor Size (Central Review, RECIST v1.1)

Presented by: Antoni Ribas

- ORR 34% (RECIST 1.1)
- 40% ORR in ipi-Naïve
- 44% ORR in treatment-naïve
- 28% ORR in ipi-treated

In patients with measurable disease at baseline by RECIST v1.1 by central review and ≥1 postbaseline assessment (n = 317). Percentage changes >100% were truncated at 100%.

Analysis cut-off date: October 18, 2013.
Time to and Durability of Response (Central Review, RECIST v1.1)

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

*Ongoing response defined as alive, progression free, and without new anticancer therapy.
Analysis cut-off date: October 18, 2013.

Presented by: Antoni Ribas
Kaplan-Meier Estimate of Overall Survival

- Median OS not reached
- 69% OS rate at 12 months (74% for IPI-N, 65% for IPI-T)
- 62% OS rate at 18 months

OS rate at 18 months is driven by the 135 patients enrolled in the nonrandomized cohorts because they have the longest follow-up duration.

Analysis cut-off date: May 2014.
Objectives

- To report updated safety, survival, and clinical activity of initial concurrent cohorts 1-3 (N=53) with additional follow-up of ~ 1 year
- To report responses in a new cohort (cohort 8) of 41 patients using Phase 2/3 dosing regimen (last patient, first treatment Nov. 2013)

Concurrent Therapy

- Induction: Nivo + IPI every 3 weeks for 4 doses (12 weeks)
- Cohorts 1, 2, 2a, 3: Nivo every 3 weeks for 4 doses then: Nivo + IPI every 12 weeks for 8 doses
- Cohort 8: Nivo 3 mg/kg every 2 weeks until disease progression

Sequential Therapy

- Prior standard ipilimumab therapy
- Cohorts 6, 7: Nivo 1 or 3 mg/kg Q2W IV until disease progression
Overall Survival for Concurrent Therapy by Dose Cohort

- 1 Yr OS 94%
- 2 Yr OS 88%
- 1 Yr OS 85%
- 2 Yr OS 79%
- 1 Yr OS 57%
- 2 Yr OS 50%

Mario Sznol, MD
### Safety Overview

#### Presented by: Mario Sznol, MD

**Table: Safety Outcomes**

<table>
<thead>
<tr>
<th>AE, %</th>
<th>Concurrent Cohorts 1-3 n=53</th>
<th>Cohort 8 n = 41</th>
<th>All Concurrent n=94</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Gr</td>
<td>Gr 3/4</td>
<td>Any Gr</td>
</tr>
<tr>
<td>All Related AEs</td>
<td>96</td>
<td>62</td>
<td>95</td>
</tr>
<tr>
<td>Select AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>43</td>
<td>9</td>
<td>34</td>
</tr>
<tr>
<td>Hepatic</td>
<td>30</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Skin</td>
<td>79</td>
<td>4</td>
<td>73</td>
</tr>
<tr>
<td>Endocrine</td>
<td>17</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Renal</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uveitis</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>26</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>21</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

- No new safety signals with 22 months of follow-up for the initial concurrent cohorts
- 22/94 (23%) patients discontinued treatment due to treatment-related adverse events
- 1/94 drug-related death in trial; fatal multi-organ failure (as a result of colitis) in cohort 8
Immune-related Adverse reactions (IrAEs)

- Checkpoint blockade inhibitors are showing benefit in multiple histologies
  - ipilimumab FDA approved for metastatic melanoma
  - REMS program created for ipilimumab: www.yervoy.com/hcp/rems.aspx

- Pembrolizumab first PD-1 inhibitor FDA approved September 2014

- Immuno-oncologic agents will soon hold a prominent place

- Knowledge of toxicities and appropriate management is essential

- Mimic autoimmune conditions and are typically managed with high dose steroids

- May require secondary immunosuppressive agents depending upon steroid response

- However, do not want to start steroids on a patient on immunotherapy UNLESS necessary
  - Call treating oncologist immediately
Most common IrAEs

• Dermatologic:
  — 40-50% pruritis, macular rash
  — <1% Steven’s Johnson syndrome

• GI:
  — ~30% Enterocolitis; severe in 5-8%
  — Can effect upper GI tract
  — Can perforate
  — Low threshold for colonoscopy

• Hepatitis
  — 2-9%
  — Both immune mediated and drug related
  — Avoid acetaminophen and ETOH

• Endocrinopathies
  — Hypophysitis (0-17%)
  — Adrenal Insufficiency
  — Thyroiditis/Grave’s or hypothyroidism

• Neuropathies
  — Rare: Sensory or motor
  — Reports of guillain barré, myasthenia gravis, aseptic meningitis, optic neuritis

• Others: uveitis, nephritis, pneumonitis, hematologic or rheumatologic toxicities, others…

Fecher et al, Oncologist, 2013
Algorithms are available

Fecher et al, Oncologist, 2013
Molecular Therapies

- RTK
- c-KIT
- IMATINIB
- SRC
- PI3K
- AKT
- PTEN
- mTOR
- BRAF
- MEK1/2
- ERK1/2
- Vemurafenib (RG7204)
- Dabrafenib (GSK2118436)
- Trametinib (GSK1120212)
- Selumetinib (AZD6244)
- Cobimetinib (GDC 0973)
MAPK: BRAF

Activating BRAF mutations:

• ~50% of melanomas

• 80% of BRAF mutations are V600E → High kinase activity

• Not sufficient for malignant transformation; present in majority of benign nevi

• Most commonly found in intermittently sun-exposed melanomas

• Rarely seen in noncutaneous melanomas

BRAF: Vemurafenib (RO5185426/PLX4032/RG7204)

Dose Extension Cohort (n=32): BRAF mutant melanoma

Response Rate = 81% (24 PR, 2CR)
PET Scans at Baseline and Day 15

Pt #69 (MDACC): PET Scans at Baseline and Day 15

#59 Peter MacCallum

Pre-treatment

Cycle 2

Cycle 4
BRIM2 - Phase II: Vemurafenib in 122 \( V600E \) BRAF mutant melanoma patients

*** 7 patients had 100% tumor shrinkage, 3 of which had cCR; 1 patient had unconfirmed CR and 3 patients had non-target lesions present

BORR = 53%

6% CR

47% PR

Sosman et al. NEJM 2012
BRIM II: Progression-free survival with vemurafenib

Sosman J et al. NEJM 2012

Med PFS = 6.8 mo
Med resp duration = 6.7 mo
Med OS 15.9 months
BRIM 3: Randomized study of Vemurafenib vs. DTIC in previously untreated metastatic melanoma

- **6 mo OS**: 
  - V: 84% [CI], 78 – 89
  - DTIC: 64% [CI] 56-73

- **Median PFS**
  - V: 5.3mo
  - DTIC: 1.6mo

- **PFS HR = 0.26**
BREAK-3: DTIC v Dabrafenib

PFS HR=0.30; p<0.0001

Median PFS:
Dabrafenib: 5.1 mos
DTIC: 2.7 mos

OS HR=0.61
(crossover to dabrafenib: 44%)

<table>
<thead>
<tr>
<th></th>
<th>Dabrafenib (n=187)</th>
<th>DTIC (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>PR</td>
<td>47%</td>
<td>5%</td>
</tr>
<tr>
<td>SD</td>
<td>42%</td>
<td>48%</td>
</tr>
</tbody>
</table>
BRAFi and Brain Metastases

9 of 10 treated patients with asymptomatic brain metastases had reduction in size of metastases; four achieved complete resolution
Cutaneous side effects of BRAFi

Squamous Cell Carcinoma/Keratoacanthoma

Photosensitivity

Eruptive nevi

Keratosis Pilaris-like eruption

Milia and Acne

Erythema Nodosum or panniculitis

Palmar plantar hyperkeratosis

Combinatorial Therapy: BRAFi+ MEKi

Flaherty et al, NEJM, 2012
COMBI-d: Investigator-Assessed PFS
Data cut August 2013*

Censored in 1st 2 months

Dabrafenib
Med. PFS 8.8 mo
6 month PFS = 57%

Dabrafenib + Trametinib
Med. PFS 9.3 mo
6 month PFS = 70%

HR 0.75 (95% CI: 0.57, 0.99)
p=0.035

*Med f/u 9 months. 42% (dab) vs 53% (dab+tram) remained on study drug at data cut

Presented by: Georgina V. Long
Important Toxicities

- **Skin**: rashes (rare DRESS syndrome), hand foot syndrome, benign growths, photosensitivity
- **Cardiac**: QTc prolongation (BRAFi), LVEF decrease and HTN (MEKi)
- **Ocular**: uveitis (BRAFi), central serous retinopathy or retinal vein occlusion (MEKi)
- **Systemic**: fever (75% in combination tx), myalgias and arthralgias, bleeding and clotting risk
- **Pulmonary**: pneumonitis (MEKi)
- **Secondary malignancies**: skin (BCC, SCC, melanoma), pancreas, colon polyps, head and neck SCC, others?

Oral cancer therapies: PLEASE communicate immediately with pt and with treating oncologist regarding continuing or stopping drug
In melanoma, there is no wild type population

Walia et al, PCMR, 2012

Hodis, Cell, 2012
Biologically driven therapeutic targeting: KIT, NRAS, and CDK4/6

**Table 2. Correlations of Response and c-Kit Aberrations**

<table>
<thead>
<tr>
<th>c-Kit status</th>
<th>No. of Patients</th>
<th>PR No.</th>
<th>PR %</th>
<th>SD No.</th>
<th>SD %</th>
<th>PR + SD No.</th>
<th>PR + SD %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>c-Kit amplification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 9</td>
<td>3</td>
<td>1</td>
<td>33.3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>33.3</td>
</tr>
<tr>
<td>Exon 11</td>
<td>17</td>
<td>6</td>
<td>35.3</td>
<td>2</td>
<td>66.7</td>
<td>18</td>
<td>100.0</td>
</tr>
<tr>
<td>Exon 13</td>
<td>9</td>
<td>3</td>
<td>33.3</td>
<td>1</td>
<td>11.1</td>
<td>4</td>
<td>44.4</td>
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<tr>
<td>Exon 17</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>40.0</td>
<td>2</td>
<td>40.0</td>
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<tr>
<td>Exon 18</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>50.0</td>
<td>3</td>
<td>50.0</td>
</tr>
<tr>
<td><strong>Multiple aberrations</strong></td>
<td>5</td>
<td>3</td>
<td>60.0</td>
<td>2</td>
<td>40.0</td>
<td>4</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Note: *Five patients harbored multiple c-Kit aberrations, each one as follows: K642E (exon 13) + amplification; I653T (exon 13) + T1940C (exon 13); F848L (exon 18) + T2576C (exon 18); L576P (exon 11) + amplification; P577H (exon 13) + N486D (exon 9).*

**Median OS:** 10.7mo

1yr OS = 51%

Results: Response

**Phase IB/II Bimimetinib (MEK162) and LEE011 in NRAS mutant melanoma**

### Overall Response

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>LEE011 + Binimetinib (N = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Confirmed PR</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Unconfirmed PR</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>11 (52)</td>
</tr>
<tr>
<td>20-30% Tumor Mass Decrease by RECIST 1.1</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Clinical benefit rate (CR + PR + SD)</td>
<td>18 (86)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Unevaluable</td>
<td>1 (NA)</td>
</tr>
</tbody>
</table>

- Several patients had early tumor shrinkage with major symptomatic improvement

*Includes 1 patient with KRAS-mutant pancreatic cancer.

**RECIST, Response Evaluation Criteria in Solid Tumors.**
Conclusions for Advanced Melanoma

• Clinical trial participation is **STILL** a standard of care in melanoma: Refer *early and often*

• Tumor genotyping is standard of care
  – Be aware of details regarding testing

• BRAFi + MEKi surpassing single agent therapy in first line

• PD-1 and PDL1 antibodies evidencing good tolerability and clinical activity

• Combination immunotherapy promising, additional data still accumulating

• **Combinatorial Therapy**
  Informed by tumor profiling, resistance mechanisms, and other predictive markers to be defined
  – Within a pathway:
    • MEK and BRAF
  – Across pathways
    • MAPK + PI3K pathway inhibitors
  – Across mechanisms of action
    • Immune therapies + molecular therapies

• Melanoma is not one size fits all, therapy selection must be tailored to the patient
Questions

1. Clinical Trials are a first line treatment option for advanced, unresectable melanoma. True or False?

2. What is a relative contraindication to treatment with ipilimumab?
   A. Baseline renal dysfunction from hypertension (Cr 1.5)
   B. Rheumatoid Arthritis
   C. Recent Radiation
   D. None of the above
Questions?

3. Patients who did not respond to ipilimumab will not respond to another immunotherapy? True or False?

4. Chemotherapy has no role in the treatment of advanced, unresectable melanoma? True or False?
IUSCC Melanoma Resources

Melanoma Program:
317-948-7449

Medical Oncology:
Leslie Fecher, MD – lafecher@iu.edu
Ted Logan, MD

Dermatology:
Lawrence Mark, MD
Elizabeth Bryant, MD

Surgery:
Plastic and Reconstructive
William Wooden, MD
317-274-0770

Surgical Oncology:
Douglas Schwartzentruber, MD
Leonidas Koniaris, MD

Radiation Oncology:
Mark Langer, MD

Dermatopathology:
Simon Warren, MD
Matthew Kuhar, MD

Melanoma Nurse Coordinators:
Melissa Koffi, RN
Lisa Freestone, RN