New Approaches for Advanced Cutaneous Malignancies of the Head & Neck

Presented by Gary I. Cohen, MD, FACP
Medical Director, Sandra & Malcolm Berman Cancer Institute at GBMC

Head & Neck Grand Rounds
May 4, 2012
Melanoma 2012

- Fastest rising incidence of any cancer over the last 3 decades
- Median age at diagnosis: 60 yrs
- Early metastatic potential
- Early and common CNS seeding
- Historic lack of effective systemic therapies until recently
- Among leading tumors in yrs of life lost

Lifetime Risk of Developing Invasive Melanoma in the US

US = United States.
Trends in Cancer Incidence: Changes 1950–2001 (Caucasians)

- Melanoma: 690.2%
- Lung: 290.1%
- Prostate: 286.2%
- Multiple Myeloma: 272.6%
- Thyroid: 257.6%
- NHL: 248.9%
- Liver: 234.3%
- Kidney: 181.7%
- Testis: 143.4%
- CNS: 135.6%
- Bladder: 97.1%
- Breast: 90.0%
- All Sites: 85.9%
- Childhood (0–14 yrs): 67.1%
- Pancreas: 35.9%
- Leukemia: 33.0%
- Esophagus: 21.2%
- Larynx: 17.8%
- Colorectal: 17.5%
- Uterus: 14.9%
- Hodgkin's Disease: 13.2%
- CNS: 13.2%
- Ovary: 2.6%
- Oral: -33.0%
- Stomach: -75.8%
- Cervix: -77.7%

*Not including in situ melanoma.
NHL = non-Hodgkin lymphoma.
Melanoma: Facts and Figures

- Approximately 76,250 new cases of melanoma and 9,180 deaths from melanoma are expected in the US in 2012.
It’s All About the Sun and UV Tanning Devices

- Use of artificial tanning devices (sun lamps or beds) has rapidly expanded in industrialized countries recently.
- As early as 1988, there were 18,000 tanning centers in the US attended by 2 million people daily.
- Melanoma risk increases with frequency of tanning device use, number of yrs used, and younger age at time of use.
- Thinning of the ozone layer, and genetics also plays a factor in risk for those with increased UV exposure.
- Familial risk usually associated with atypical nevi.

UV = ultraviolet rays.
de Souza et al, 2004; Randle, 1997.
The ABCs of Melanoma Diagnosis

A - Symmetry
One half of the lesion is shaped differently than the other

B - Border
The border of the lesion is irregular, blurred, or ragged

C - Color
Inconsistent pigmentation, with varying shades of brown and black

D - Diameter
> 6 mm, or a progressive change in size

E - Evolution
History of change in the lesion

Courtesy of ACS, 2010.
# Morphologic Types of Melanoma

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial spreading melanoma</td>
<td>60%–70%</td>
<td>Flat during early phase; notching, scalloping, areas of regression</td>
</tr>
<tr>
<td>Nodular melanoma</td>
<td>15%–30%</td>
<td>Darker and thicker than superficial melanoma; spreading, rapid onset; commonly blue-black or blue-red (5% amelanotic)</td>
</tr>
<tr>
<td>Lentigo maligna melanoma</td>
<td>~ 5%</td>
<td>Enlarge slowly; usually large, flat, tan, or brown</td>
</tr>
<tr>
<td>Acral lentiginous melanoma</td>
<td>Uncommon</td>
<td>On soles, palms, beneath nail beds; usually large, tan or brown; irregular border; subungual melanoma more common in older, dark-skinned people</td>
</tr>
<tr>
<td></td>
<td>Asians (46%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>African Americans (70%)</td>
<td></td>
</tr>
<tr>
<td>Desmoplastic melanoma</td>
<td>1.7%</td>
<td>Rare, locally aggressive, occur primarily on head and neck in elderly</td>
</tr>
</tbody>
</table>
Melanoma Staging

--Thickness
--Ulceration
--Mitoses
--(NOT Clark’s level)
--T (< 1 mm, > 4 mm), N, M1a,b,c

Other Features
--Clinical: gender, location, age
--Pathology: regression, lymphoid infiltration, etc
--Nodal status
Precise Surgical Staging
Lymphatic Mapping of Melanoma:
The Best Opportunity to Cure Melanoma Presently Lies in the Adjuvant Setting

Balch, C. M. et al. MELANOMA STAGING AND PROGNOSIS 2009
Adjuvant Therapy of Melanoma: History

- Microbial/Chemical Immunomodulators (BCG, Levamisole)
- Chemotherapy, Chemobiotherapy, BMT
- Vaccines
  - Whole Cell & Cell-derived Antigen
  - Peptide and Protein Antigen (T Cell)
  - Ganglioside Antigen (B Cell)
- Passive (Antibody) & Adoptive (Cellular) Transfer
- Interferon
E1684: Study Design

Randomization
N = 287
(within 56 days)
(all with ELND)

Induction: 20 MIU/m² IV 5 × wkly × 4 wks
Maintenance: 10 MIU/m² SC TIW × 48 wks
Design: Exponential model, HR analysis
Stratification: AJCC stage groupings

Observation
52 wks

IFN-α2b

Induction
4 wks

Maintenance
48 wks

IFN = interferon-alfa 2b; ELND = elective lymph node dissection; SC = subcutaneous; TIW = three times a week; HR = hazard ratio; AJCC = American Joint Committee on Cancer.

Kirkwood et al, 1996.
E1684: RFS (eligible cases) at 6.9-yr Median Follow-Up

Treatment Groups (n = 280)

IFN-α2b  Observation

HR for Relapse w/o IFN 1.43
Significant at $p = .002$

RFS = relapse-free survival.
Kirkwood et al, 1996.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. Patients</th>
<th>No. Relapsed</th>
<th>Median yr</th>
<th>p Value</th>
<th>5-yr RFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-α2b</td>
<td>143</td>
<td>90</td>
<td>1.72</td>
<td>&lt; .01</td>
<td>37%</td>
</tr>
<tr>
<td>Observation</td>
<td>137</td>
<td>103</td>
<td>0.98</td>
<td>&lt; .01</td>
<td>26%</td>
</tr>
</tbody>
</table>
Intergroup E1690 Phase III Trial of High or Low Dose IFN-α2b Vs. Observation

Goal: Determine if low-dose IFN-α2b for 2 yrs is effective as high-dose IFN-α2b for 1 yr

Design: Cure rate model, HR analysis

Stratification: AJCC stage groupings and number of positive nodes

Randomization
N = 642 (within 70 days)

High-dose IFN-α2b × 1 yr
Low-dose IFN-α2b × 2 yrs
Observation

Intergroup E1694 Phase III Trial: GM2-KLH/QS-21 (GMK vaccine) Vs. High-Dose IFN-α2b

880 Patients
T4 N0 or
T(any)N1–2

GM2-KLH/QS-21 (GMK) x 96 wks

High-Dose IFN-α2b x 52 wks

- Primary end points: Survival, relapse-free interval
- Secondary analysis: Antibody responses, in relation to clinical course

KLH = keyhole limpet hemocyanin.
Updated Durable RFS Is Highly Significant for E1684-1690-1694

**E1684**

IFN vs. Obs: $p_2 = .02$, $p_1 = .01$, HR = 1.38

**E1690**

IFN vs. Obs: $p_2 = .09$, HR = 1.24

**E1694**

IFN vs. GMK: $p_2 = .006$, HR = 1.33

Goals of Therapy: Reduce Toxicity
Is 1 yr of IFN Necessary?
Dose, Route, and Duration of IFN Therapy

- All trials of IFN-α2b with durable RFS and OS impact utilized IV induction at 20MU/m² ($C_{\text{max}} > 10,000$ u/mL)
- Is 1 month of IV IFN-α2b necessary and sufficient?
  - Intergroup E1697
  - Neoadjuvant trial UPCI 00-008

IV = intravenous.
Relapse-free survival (n=975)

Median RFS (95% CI), years
Obs (n=481): 7.8 (5.8, 9.8)
IFN (n=494): 7.3 (7.0, 9.5)
p=0.690*

*Stratified log-rank test

Agarwala SS et al. Abs #8505
Adjuvant Therapy of High-risk Melanoma

- Interferon Trials
  - High dose for 1 year
  - Intermediate dose IFN
  - Low dose IFN

- One month high dose induction only
  - ECOG Trial E 1697

- PEG IFN for stage III melanoma
  - EORTC Trial 18991
Metastatic Melanoma

- High dose Interleukin-2
- Chemotherapy (Single agent, combinations)
- Bio-chemotherapy
- Anti-CTLA4 antibodies
- BRAF inhibitors
- New agents

NCCN, 2011.
HD-IL2 Treatment Regimen

Course of Treatment

- **rIL2**
  - 600,000 IU/kg
  - q8hrs by 15-min infusion
  - Max of 14 doses

- **REST**

- **rIL2**
  - 600,000 IU/kg
  - q8hrs by 15-min infusion
  - Max of 14 doses

5 days  
Cycle 1

9 days  
Cycle 2

5 days  
Cycle 2

Maximum number of doses per course: 28

Proleukin® prescribing information, 2011.
IL-2 Side Effects
Physiologic Categories

- Flu-like (constitutional symptoms)
- Capillary leak syndrome (CLS)
- Cardiovascular
- Pulmonary
- Renal
- Gastrointestinal

- Hepatic
- Neurologic
- Dermatologic
- Hematologic
- Metabolic
Kaplan-Meier Plots of Response Durations for Patients Who Achieved CR, PR, or Any Response With HD-IL2

- CR: 6% (17 pts)
- OR: 16% (33 pts)
- PR: 10% (26 pts)
Metastatic Melanoma: Systemic Chemotherapy

- Cytotoxic chemotherapy
  - DTIC – FDA-approved in metastatic melanoma 1975
  - TMZ – similar activity to DTIC
    • Approval attempted in 1995, not FDA-approved
  - Carboplatin/Paclitaxel – activity noted in PRISM and E2603, but never compared to DTIC/TMZ
    • Not FDA-approved

- Chemo-immunotherapy (biochemotherapy)

DTIC = dacarbazine; TMZ = temozolomide.
E3695: Survival Data

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total</th>
<th>Dead</th>
<th>Alive</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td>195</td>
<td>183</td>
<td>12</td>
<td>8.7 months</td>
</tr>
<tr>
<td>BCT</td>
<td>200</td>
<td>188</td>
<td>12</td>
<td>9.0 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial/Author</th>
<th>Drug/Regimen</th>
<th>N</th>
<th>RR (%)</th>
<th>Median Survival (mos)</th>
<th>Median PFS (mos)</th>
<th>Comments/Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intergroup 3695 (Atkins et al, 2003)</td>
<td>CVD</td>
<td>201</td>
<td>11.9</td>
<td>9.1</td>
<td></td>
<td>No survival difference</td>
</tr>
<tr>
<td></td>
<td>CVD/IFN/IL-2</td>
<td>204</td>
<td>16.6</td>
<td>8.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chapman et al, 1999</td>
<td>Dartmouth Regimen</td>
<td>119</td>
<td>18.5*</td>
<td>7.7†</td>
<td></td>
<td>No difference in survival</td>
</tr>
<tr>
<td></td>
<td>DTIC</td>
<td>121</td>
<td>10.2*</td>
<td>6.3†</td>
<td></td>
<td>DTIC remains reference std</td>
</tr>
<tr>
<td>Middleton et al, 2000</td>
<td>DTIC</td>
<td>149</td>
<td>12.1†</td>
<td>6.4†</td>
<td></td>
<td>TMZ = DTIC</td>
</tr>
<tr>
<td></td>
<td>TMZ</td>
<td>156</td>
<td>13.5†</td>
<td>7.7†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bedikian et al, 2006</td>
<td>DTIC</td>
<td>385</td>
<td>7.5</td>
<td>7.8</td>
<td>1.6</td>
<td>RR Improved OS = NS</td>
</tr>
<tr>
<td></td>
<td>DTIC + Oblimersen</td>
<td>386</td>
<td>13.5</td>
<td>9</td>
<td>2.6</td>
<td></td>
</tr>
</tbody>
</table>

*Assessable for response (n = 108 for Dartmouth and n = 118 for DTIC).
†All patients evaluated on ITT basis.
CVD = cisplatin, vinblastine, dacarbazine; RR = response rate; Dartmouth regimen = dacarbazine, cisplatin, carmustine, tamoxifen; PFS = progression-free survival; NS = not significant.
Ipilimumab is a member of a novel class of immunotherapeutic antibodies.

1) Co-stimulation via CD28 ligation transduces T-cell activating signals.

2) CTLA-4 ligation on activated T cells down-regulates T-cell responses.

3) Blocking CTLA-4 ligation enhances T-cell responses.

MHC = major histocompatibility complex; TCR = T-cell receptor; APC = antigen presenting cell. Image adapted from Fong et al, 2008.
Ipilimumab Registration Trials

- **Second-line MDX010-20 trial HLA-A2 positive (N = 650)**
  - 3 arms 3:1:1 (ipilimumab/gp100 vaccine, ipilimumab alone, gp100 alone)
  - First study in metastatic melanoma to demonstrate OS benefit in large randomized placebo-controlled trial

- **First-line CA184-024 trial, randomized placebo control (N = 500)**
  - Ipilimumab/DTIC vs. placebo/DTIC
  - Recently reported as having positive OS (ipilimumab/DTIC combination vs. DTIC)

Ipilimumab Overall Survival Advantage

Comparison | HR   | p Value |
------------|------|---------|
Arms A vs. C | 0.68 | .0004   |
Arms B vs. C | 0.66 | .0026   |

Ipilimumab Plus DTIC Vs. DTIC: OS

Wolchok et al, 2011.

- HR (95% CI): 0.72 (0.59–0.87)
- Median OS: 11.2 vs 9.1 months
- P value: 0.0009
Unique Kinetics of Responses in Patients Treated With Ipilimumab

Pre-treatment

Four blinded doses ipilimumab

Wk 12 (10/06)

No drug

12/06

Four 10 mg/kg doses ipilimumab

5/07

Images courtesy Dr. Wolchok.
Ipilimumab Patterns of Response

Screening

Week 12: swelling & progression

Week 14: improved

Week 16: continued improvement

Week 72: complete remission

Week 108: complete remission

Maggon, 2011.
Toxicity management

Frequent immune-related side effects, sometimes severe

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>All grade %</th>
<th>Grade 3 -4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>50-70</td>
<td>0-4</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>30-45</td>
<td>8-25</td>
</tr>
<tr>
<td>hepatitis</td>
<td>3-10</td>
<td>3-8</td>
</tr>
<tr>
<td>endocrine</td>
<td>5-10</td>
<td>1-5</td>
</tr>
</tbody>
</table>
Anti-CTLA-4 Abrogating Antibodies for Melanoma

- First therapy ever to show a survival advantage in either pre-treated or untreated stage IV melanoma
- Unique spectrum of side effects that are immune related
- Unusual kinetics of regression that has caused the promulgation of irRC
- Potential for many different combinations
- Optimal dosing not clear, although there are dose-limiting side effects to consider
- Utility of maintenance beyond 4 dose induction is unknown

CTLA-4 = cytotoxic T-lymphocyte antigen-4; irRC = immune-related response criteria.
### Phase I/II Trial of Sorafenib in Combination With Carboplatin/Paclitaxel in Melanoma

<table>
<thead>
<tr>
<th>Best Response (RECIST)</th>
<th>Melanoma Subset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>1 (&lt; 1%)</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>27 (26%)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>61 (58%)</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Not Assessable</td>
<td>10 (10%)</td>
</tr>
</tbody>
</table>

**85% Disease Control Rate (CR + PR + SD)**

BRAF Inhibitors Block the Activity of the Kinase Domain in Mutant BRAF

- BRAF inhibitors selectively block the kinase domain in mutant BRAF
- Constitutive activation arrested
- Cell proliferation ↓
- Cell survival ↓
- Tumor regression

BRIM2: Tumor Regression (Target Lesions) Occurred in Majority of Patients (IRC)

Individual Patients Treated With Vemurafenib

Percent Change From Baseline in Diameter of Target Lesion (%)

Disease Stage
- M1a
- M1b
- M1c

7 confirmed CR. Ribas et al, 2011.
Median OS Not Reached

OS at 6 mos 77% (95% CI: 70, 85)
12 mos 58% (95% CI: 49, 67)

Ribas et al, 2011.
BRIM2: Tumor Responses by IRC

- ORR 53% by IRC
- ORR 57% by investigator assessments (INV)
- RR, including unconfirmed, 69% (INV)

INV = investigator; SD = stable disease.
Ribas et al, 2011.
Vemurafenib Phase I: AEs in > 5% of the Study Patients Receiving the MTD Dose

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>960 mg (n = 32)</th>
<th>960 mg (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10 (31)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Rash</td>
<td>7 (22)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>cuSCC/KA</td>
<td>0</td>
<td>10 (31)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (12)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (6)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Photosensitivity Reaction</td>
<td>4 (12)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Palmar-Plantar Dysesthesia</td>
<td>2 (6)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>2 (6)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Rashes were evenly distributed among the face or neck, trunk, and extremities
- Among all dose levels, 4 patients had a grade 4 AE

  Elevated γ-glutamyltransferase levels (2), fatigue (1), and reversible pancytopenia (1)

AEs = adverse events; MTD = maximum tolerated dose; cuSCC = cutaneous squamous cell carcinoma; KA = keratoacanthoma. Flaherty et al, 2010.
BRIM3: PFS (12/30/10 Cutoff)

HR 0.26  
(95% CI: 0.20–0.33)  
Log-rank $p < .0001$

No. Patients in Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Dacarbazine (n = 274)</th>
<th>Vemurafenib (n = 275)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (mos)</td>
<td>0  1  2  3  4  5  6  7  8  9  10  11  12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>274 213 85 48 28 16 10 6 3 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>275 268 211 122 105 50 35 16 4 3</td>
<td></td>
</tr>
</tbody>
</table>

Median OS 15.9 months (95% C.I 11.6-18.3)
Melanoma

NRAS  
CRAF  
BRAF

MEKi

BRAF  
CRAF

Normal or RAS Mutant Cell

NRAS

BRAF

CRAF

MEK

ERK

MEK

ERK
Melanoma is not one disease

B-RAF: 50%
c-kit: 5-10%
c-kit: 10-20%
c-kit: 15-30%
# Clinically Indicated Molecular Testing in Advanced Melanoma

- Recommendations based upon tests with therapeutic, prognostic, or diagnostic value for patient management

<table>
<thead>
<tr>
<th>Clinical/Pathologic Subtype</th>
<th>1st step</th>
<th>2nd step</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous (Non-CSD)</td>
<td>$BRAF \pm NRAS$</td>
<td>$KIT$</td>
</tr>
<tr>
<td>Cutaneous (CSD)</td>
<td>$BRAF \pm NRAS$</td>
<td>$KIT$</td>
</tr>
<tr>
<td>Acral</td>
<td>$BRAF, KIT \pm NRAS$</td>
<td>-</td>
</tr>
<tr>
<td>Mucosal</td>
<td>$BRAF, KIT \pm NRAS$</td>
<td>-</td>
</tr>
<tr>
<td>Uveal</td>
<td>Gene Expression Profiling or Monosomy 3 Determination*</td>
<td>-</td>
</tr>
<tr>
<td>Melanoma from an Unknown Primary</td>
<td>$BRAF, NRAS$</td>
<td>$KIT; GNAQ, GNA11$, Monosomy 3</td>
</tr>
</tbody>
</table>

*Prognostic tests for metastatic risk; they do not have a defined role in patients with metastatic disease.

Non-CSD = Non-chronic sun-damaged; CSD = Chronic sun-damaged
“-”Insignificant number reported; “?” Not yet reported

Oncogenic cKIT Mutations

- Increased copy number
- Oncogenic mutation
- Amplification found
- Exon 9,11 mutations account for most mutations that respond
- No overlap with NRAS/BRAF
- 3% of all melanomas

~ 16%–40% acral/mucosal
~ 30% with solar elastosis
~ 8% conjunctival
~ 2% cutaneous
~ 0% choroidal
~ 0% without solar elastosis

Adapted from Hocker et al, 2008; Curtin et al, 2006; Smalley et al, 2009; Beadling et al, 2008.
Metastatic Melanoma
The New Therapeutic Paradigm

- Test the tumor: b-raf
  - c-kit, n-ras for clinical trials

- Pick therapy based on b-raf status
  - B-raf positive (mutant)
    - Vemurefenib
    - Immunotherapy with ipilimumab or IL-2 for selected patients
  - Braf negative (wild type) – ipilimumab, IL-2
  - Braf positive, fails b-raf therapy
    - Ipilimumab/IL-2
    - Chemotherapy
  - ALWAYS consider clinical trials
Melanoma—treatment for advanced disease

- **Adjuvant therapy**
  - High dose IFN is the standard of care
  - E1697: short course IFN not effective
  - EORTC18991: PEG IFN effective, ? less toxic

- **Metastatic disease**
  - Chemotherapy works in small number of patients
  - HD-IL2, great results in few patients, huge toxicity profile
  - Anti-CTLA4 antibodies
  - BRAF inhibitors
  - New agents

ASCO = American Society of Clinical Oncology; EORTC = European Organisation for Research and Treatment of Cancer; HD-IL2 = high dose interleukin-2; CTLA4 = cytotoxic T-lymphocyte antigen 4. NCCN, 2011.