Metastatic Malignant Melanoma: significant treatment advances

Karl D. Lewis, MD
Associate Professor of Medicine
Division of Medical Oncology
Cutaneous Oncology Program
University of Colorado Denver

Lifetime Risk of Developing Invasive Melanoma in the US


What’s the big deal? It’s just a skin cancer!

Average Years of Life Lost per Malignancy

Data Source: National Centers for Health Statistics
Can you believe
This maniac?

No sunscreen

Melanoma survival is related to stage of disease

The Problem…

- Metastatic melanoma is a bad disease

“Melanoma is the tumor that gives cancer a bad name.”

– George Canellos, Dana-Farber Cancer Institute

Overall Survival for Metastatic Melanoma

<table>
<thead>
<tr>
<th>Year Range</th>
<th>N</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>1971-1978</td>
<td>462</td>
<td>8.1 mo</td>
</tr>
<tr>
<td>1979-1986</td>
<td>748</td>
<td>7.3 mo</td>
</tr>
<tr>
<td>1987-1993</td>
<td>311</td>
<td>7.0 mo</td>
</tr>
</tbody>
</table>

There was no significant improvement in overall survival for metastatic melanoma in over 20 years

FDA Approved Drugs in Use for Stage IV Melanoma

- **Dacarbazine (DTIC)**
  - Response rate: <10% in unselected stage IV melanoma patients
  - No proven impact on survival

- **High-dose IL-2**
  - Response rate: 16% in highly selected stage IV melanoma patients
  - Durable responses: ~5%

**Objective responses to traditional therapies were very infrequent.**

Regression of Primary
Vitiligo

Survival for the whole study population (270 patients) treated with high-dose IL2

Complete response to IL-2

2011 Year of Melanoma

- Ipilimumab
- Vemurafenib
Blockade of PD-1 or CTLA-4 Signaling in Tumor Immunotherapy.

**Phase III Trial of Ipilimumab ± gp100 Vaccine Vs. gp100 Vaccine Alone: MDX010-20**

- Pretreated Metastatic Melanoma (N = 676)

| Randomize | Ipilimumab + gp100 (n = 403) | Ipilimumab + Placebo (n = 137) | gp100 + Placebo (n = 136) |

- Primary end point: OS
- Secondary end points: ORR, DOR, PFS

OS = overall survival; ORR = overall response rate; DOR = duration of response; gp100 = glycoprotein 100; PFS = progression-free survival

Kaplan-Meier Analysis of Survival

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

Pooled OS Analysis Including EAP Data: 4846 Patients

Median OS (95% CI): 9.5 (9.0–10.0)

3-year OS Rate (95% CI): 21% (20–22%)
**OS Relative to Historical Data**

- **Historical controls**
  - Phase II: 1278 patients in 42 cooperative group trials from 1975 to 2005
  - Phase III: 3739 patients in 10 trials from 1999 to 2011

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**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.
Blockade of PD-1 or CTLA-4 Signaling in Tumor Immunotherapy.

### PD-1/PD-L1 inhibiting reagents in clinical development

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Class</th>
<th>$K_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1</td>
<td>Nivolumab (MDX1106, BMS936558, BMS-ONO)</td>
<td>IgG4 fully human antibody</td>
<td>3 nM</td>
</tr>
<tr>
<td></td>
<td>Lambrolizumab (MK-3475, Merck)</td>
<td>IgG4 engineered humanized antibody</td>
<td>29 pM</td>
</tr>
<tr>
<td></td>
<td>Pidilizumab (CT-011, CureTech-Teva)</td>
<td>IgG1 humanized antibody</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>AMP-224 (Amplimmune-GSK)</td>
<td>Fc-PD-L2 fusion protein</td>
<td>-</td>
</tr>
<tr>
<td>PD-L1</td>
<td>BMS935559 (MDX-1105, BMS-ONO)</td>
<td>IgG4 fully human antibody</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>MPDL3280A (Genentech)</td>
<td>IgG1 engineered fully human antibody</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>MEDI4736 (MedImmune, AZ)</td>
<td>IgG1 engineered fully human antibody</td>
<td>-</td>
</tr>
</tbody>
</table>

### Nivolumab single agent therapy: Best Change In Target Lesions to First RECIST Progression

*Nonconventional responders*

Horizontal line at $-30\%$ = threshold for defining objective response (partial tumor regression) in absence of new lesions or non-target disease according to RECIST. Horizontal line at $+20\%$ indicates the threshold for determination of progressive disease according to RECIST.

*Sznol et al. ASCO 2013*
MK 3475 single agent therapy:
Maximum Change From Baseline in Tumor Size
(Independent Central Review per RECIST 1.1)

Individual Patients Treated With Pembrolizumab

Ribas et al. ASCO 2013

Nivolumab + Ipilimumab combination therapy:
Best Responses in Concurrent Cohorts
(WHO response criteria)

Wolchok et al. ASCO 2013

After ~13 months of follow-up, for all concurrent cohorts, 90% of all responding patients continue to respond as of Feb 2013.
MK 3475 Clinical Activity, Patient 015-105

Baseline: April 13, 2012

April 9, 2013

72-year-old male with symptomatic progression after bio-chemotherapy, HD IL-2, and ipilimumab

Images courtesy of A. Ribas, UCLA.

Conclusions – Immune therapy

• Immune therapy is an effective treatment for melanoma resulting in durable responses in some patients
• Toxicity can be great
• Newer agents (PD-1 antibodies) may result in larger numbers of patients benefiting
• Combinations of agents (Ipi + PD-1) may result in greater benefit still
Molecularly targeted therapies

- Proof of concept from drugs such as \textit{imatinib}:
  - Approved for treatment of CML
  - 9;22 translocation (BCR/ABL)
  - High rates of response and remission

- Would this work in melanoma?
The Targets

BRAF INHIBITORS

Vemurafenib
Dabrafenib

Responses BRIM 2

Figure 1. Objective Tumor Responses with Vemurafenib, According to Metastatic Stage.
PET Scans at Baseline and Day 15 After Vemurafenib

PET = positron emission tomography.

Chapman, 2009.

Progression-free survival (12/30/10 cutoff)

Hazard Ratio 0.26
(95% CI; 0.20 - 0.33)
Log-rank P<0.0001

Progression-free survival (%)

Vemurafenib (N=275)
Dacarbazine (N=274)
Median 1.6 mo
Median 5.3 mo

No. of patients in follow up
Dacarbazine 274 213 85 48 28 16 10 6 3 0
Vemurafenib 275 268 211 122 105 50 35 16 4 3

Chapman et al. 2011
Comparison of Maximum Response With Vemurafenib and Dabrafenib


Examples of Brain Metastases Responses to Dabrafenib

Baseline Week 8

Baseline Week 32
<table>
<thead>
<tr>
<th></th>
<th>Vemurafenib Ph 3 (n=336)</th>
<th>Dabrafenib Ph 3 (n=187)</th>
<th>LGX 818 Ph 1 (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkeratoses</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Rash</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Alopecia</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>SCC/KA</td>
<td>19%</td>
<td>10%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>52%</td>
<td>2%</td>
<td>X</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>56%</td>
<td>19%</td>
<td>31.5%</td>
</tr>
<tr>
<td>Elevated Liver Enzymes</td>
<td>26%</td>
<td>&lt;10%</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18% (G3 0%, SAE 1%)</td>
<td>16% (G3 3%, SAE 5%)</td>
<td>5.6%</td>
</tr>
<tr>
<td>Plantar-Palmar Hyperkeratoses</td>
<td>7%</td>
<td>21%</td>
<td>48.2%</td>
</tr>
<tr>
<td>Dose Reduction</td>
<td>38%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Discontinuation</td>
<td>6%</td>
<td>3%</td>
<td></td>
</tr>
</tbody>
</table>

**Photosensitivity**

![Image of photosensitive skin](image-url)
Histologic Evidence of BRAF Resistance

Day -1  Day 15  At progression

pERK (IHC): Re-activation of MAPK pathway at progression

Mechanism of Resistance to BRAF Inhibition

RAS  \[\rightarrow\]  BRAF V600E  \[\rightarrow\]  MEK 1/2  \[\rightarrow\]  ERK 1/2  \[\rightarrow\]  Cell Proliferation

NRAS  \[\rightarrow\]  CRAF

Vemurafenib  \[\rightarrow\]  Dabrafenib  \[\rightarrow\]  LGX818  \[\rightarrow\]  Trametinib  \[\rightarrow\]  Cobimetinib  \[\rightarrow\]  MEK 1/2
OVERCOMING RESISTANCE

BRAF + MEK INHIBITION

Dabrafenib + Trametinib
Vemurafenib + Cobimetinib
Vemurafenib

February 2010

May 2010

Combined BRAF & MEK inhibition: Preclinical data & PET scan response

- Preclinical data support combined inhibition of BRAF and MEK:
  - Prevents the emergence of resistance
  - Overcomes acquired resistance

![Graph showing tumor volume over time with comparison between Vemurafenib, MEKi, and combination therapy.]

Vemurafenib + MEKi shows significant reduction in tumor volume compared to other treatments.

Images showing PET scan response:
- Week 1
- Week 2
- Week 4
- Week 6
Combined BRAF & MEK inhibition
Clinical Trials:
COMBI-d
COMBI-v
CoBRIM
CoBRIM


PFS Median:

- D+T: 11.4 m
- Vem: 7.3 m
- HR: 0.56

COMBI-v: Overall Survival

Median Follow-up: D + T = 11 months and Vem = 10 months

PFS Median:

- D+T: 11.4 m
- Vem: 7.3 m
- HR: 0.56

Died, n (%):

- D+T (n = 352): 100 (28)
- Vem (n = 352): 122 (35)

Median, months:

- D+T (95% CI): 18.3-NR
- Vem (95% CI): 17.2-NR

Adjusted HR (95% CI):

- 0.69 (0.53-0.99)

2-sided P-value (boundary):

- 0.005 (<0.0214)
Conclusions – Targeted Therapies

• Very high response rates in select patients with specific mutation
• Resistance is a major problem
• Overcoming resistance is an area of active research
• Combination of BRAF + MEK inhibitor now standard therapy

The Problem…

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The Problem...

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Conclusions - Melanoma

- Major advances in the last few years for patients with advanced melanoma
  - Immune therapy
  - Targeted therapy
- For the first time we are able to alter the natural history of this disease
- Research continues:
  - Further delay and/or prevent resistance
  - Identifying which patients will respond to immune therapy.
Melanoma

• Where we are:
  – BRAFi + MEKi combo – SOC for BRAF-mutated pts
  – Ipilimumab and PD-1 Abs
• Where we are going:
  – Ipilimumab + PD-1 Abs
  – PD-1 Abs + BRAF/MEK combo

What are the costs?!

• Vemurafenib: $14 k/month
• Dabrafenib: $8k/month
• Trametinib: $9k/month

• Ipilimumab: ~$12.5k/dose (drug only)
• Pembrolizumab: ~$7.5k/dose (drug only)