Treatment of Tumors Resistant to PD-1 inhibitors

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Overview

• Metastatic melanoma as a model disease for immunotherapy, a disease that affects ~10,000 individuals per year in the US

• Advances in immune therapy in the past decade

• Current challenges

• New initiatives to overcome resistance to immune checkpoint inhibitors
James P. Allison • Tasuku Honjo
“for their discovery of cancer therapy by inhibition of negative immune regulation”
# Key Randomized Trials for Stage IV Melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial Regimen</th>
<th>No. of Patients</th>
<th>Response Rate %</th>
<th>Median Survival mo</th>
</tr>
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<tr>
<td>Costanzi et al.</td>
<td>Carmustine, hydroxyurea, and dacarbazine with or without BCG versus</td>
<td>256</td>
<td>29</td>
<td></td>
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<tr>
<td></td>
<td>Dacarbazine and BCG</td>
<td>130</td>
<td>18</td>
<td>6.9</td>
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<tr>
<td>Buzaid et al.</td>
<td>Cisplatin, vinblastine, and dacarbazine versus</td>
<td>46</td>
<td>24</td>
<td>6.0</td>
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<tr>
<td></td>
<td>Dacarbazine</td>
<td>45</td>
<td>11</td>
<td>7.0</td>
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<td>Chapman et al.</td>
<td>Cisplatin, dacarbazine, carmustine, and tamoxifen versus Dacarbazine</td>
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<td>7.0</td>
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<td>Cocconi et al.</td>
<td>Dacarbazine and tamoxifen versus Dacarbazine</td>
<td>60</td>
<td>28‡</td>
<td>10.7‡</td>
</tr>
<tr>
<td></td>
<td>Dacarbazine</td>
<td>52</td>
<td>12</td>
<td>6.4</td>
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<tr>
<td>Rusthowen et al.</td>
<td>Cisplatin, dacarbazine, carmustine, and tamoxifen versus</td>
<td>98</td>
<td>30</td>
<td>Men, 6.4; women, 6.9</td>
</tr>
<tr>
<td></td>
<td>Cisplatin, dacarbazine, and carmustine</td>
<td>97</td>
<td>21</td>
<td>Men, 6.4; women, 7.1</td>
</tr>
<tr>
<td>Falkson et al.</td>
<td>Dacarbazine and interferon alfa versus Dacarbazine</td>
<td>30</td>
<td>53</td>
<td>17.6§</td>
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<tr>
<td></td>
<td>Dacarbazine</td>
<td>30</td>
<td>18</td>
<td>9.6</td>
</tr>
<tr>
<td>Falkson et al.</td>
<td>Dacarbazine, interferon alfa with or without tamoxifen versus Dacarbazine</td>
<td>126</td>
<td>16</td>
<td>With tamoxifen, 9.5; without tamoxifen, 9.3; With tamoxifen, 8.4; without tamoxifen, 10.0</td>
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<tr>
<td></td>
<td>Dacarbazine with or without tamoxifen</td>
<td>129</td>
<td>21</td>
<td></td>
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<tr>
<td>Kellholz et al.</td>
<td>Interleukin-2 (decrescendo regimen) and interferon alfa versus</td>
<td>66</td>
<td>18</td>
<td>9.0</td>
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<tr>
<td></td>
<td>Cisplatin, interleukin-2, and interferon alfa</td>
<td>60</td>
<td>33; overall survival same</td>
<td>9.0</td>
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<tr>
<td>Rosenberg et al.</td>
<td>Cisplatin, dacarbazine, and tamoxifen</td>
<td>52</td>
<td>27</td>
<td>15.8</td>
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<tr>
<td></td>
<td>Cisplatin, dacarbazine, tamoxifen, high-dose interleukin-2, and interferon alfa</td>
<td>50</td>
<td>44; overall survival worse</td>
<td>10.7</td>
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<tr>
<td>Eton et al.</td>
<td>Cisplatin, vinblastine, and dacarbazine versus</td>
<td>92</td>
<td>25</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>Cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa (sequential)</td>
<td>91</td>
<td>48</td>
<td>11.8</td>
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<tr>
<td>Kellholz et al.</td>
<td>Cisplatin, dacarbazine, interferon alfa versus</td>
<td>180</td>
<td>23</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>Cisplatin, dacarbazine, interferon alfa and interleukin-2 versus</td>
<td>183</td>
<td>21</td>
<td>9.0</td>
</tr>
<tr>
<td>Atkins et al.</td>
<td>Cisplatin, vinblastine, and dacarbazine versus</td>
<td>201</td>
<td>11</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td>Cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa (concurrent)</td>
<td>204</td>
<td>17</td>
<td>8.4</td>
</tr>
</tbody>
</table>

*All study data are taken from Atkins et al.*

**BCG denotes bacille Calmette–Guérin.

‡ P = 0.03.

§ P = 0.02.

§§ P = 0.01.
Drugs and regimens approved since 2011

**BRAFi/MEKi for Braf mutant melanoma only:**
- Vemurafenib
- Vemurafenib + cobimetinib
- Dabrafenib
- Dabrafenib + trametinib (both for metastatic and adjuvant therapy)
- Binimetinib + encorafenib

**Immune therapies:**
- Ipilimumab (both for metastatic and adjuvant therapy)
- Nivolumab (both for metastatic and adjuvant therapy)
- Pembrolizumab (both for metastatic and adjuvant therapy)
- Ipilimumab + nivolumab
- TVEC
Overall survival in patients with metastatic melanoma prior to 2011

Surgery\(^1\)

Chemotherapy\(^2,3\)


Presented by:
Alex Menzies
ASCO 2017
Overall Survival: Metastatic Melanoma Phase III Studies – A Menzies, ASCO 2017

## PD-1 inhibitors: Phase I nivolumab trial RESPONDERS TIME ON STUDY

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Diagnosis</th>
<th>Time on Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td>Melanoma</td>
<td>18+ months</td>
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<tr>
<td></td>
<td>Melanoma</td>
<td>8+ months</td>
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<td></td>
<td>Melanoma</td>
<td>9+ months</td>
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<tr>
<td></td>
<td>Melanoma</td>
<td>9+ months</td>
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<td></td>
<td>Melanoma</td>
<td>6+ months</td>
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<tr>
<td><strong>3</strong></td>
<td>Melanoma</td>
<td>14+ months</td>
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<td></td>
<td>Melanoma</td>
<td>7+ months</td>
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<tr>
<td></td>
<td>Melanoma</td>
<td>6+ months</td>
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<tr>
<td></td>
<td>Melanoma</td>
<td>5+ months</td>
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<tr>
<td></td>
<td>Melanoma</td>
<td>5+ months</td>
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<tr>
<td><strong>10</strong></td>
<td>Melanoma</td>
<td>12+ months</td>
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<td></td>
<td>Melanoma</td>
<td>8+ months</td>
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<td></td>
<td>Melanoma</td>
<td>8+ months</td>
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<tr>
<td></td>
<td>Melanoma</td>
<td>8+ months</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>7+ months</td>
</tr>
</tbody>
</table>

As of May, 2010

Sznol, et al., ASCO 2010
Ipilimumab + Nivolumab (Wolchok, Kluger... Sznol, NEJM 2013)

CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4; MHC = major histocompatibility complex; PD-1 = programmed death-1; PD-L1 = programmed death ligand 1; TCR = T-cell receptor.
Phase 1 CA209-004 Study Design

Concurrent Therapy

### Cohort 1
(N = 14)
- Nivo 0.3 + Ipi 3
- Q3W x 4
- Nivo 0.3
- Q3W x 4
- Nivo 0.3 + Ipi 3
- Q12W x 8

### Cohort 2
(N = 17)
- Nivo 1 + Ipi 3
- Q3W x 4
- Nivo 1
- Q3W x 4
- Nivo 1 + Ipi 3
- Q12W x 8

### Cohort 3
(N = 6)
- Nivo 3 + Ipi 3
- Q3W x 4
- Nivo 3
- Q3W x 4
- Nivo 3 + Ipi 3
- Q12W x 8

### Cohort 2a
(N = 16)
- Nivo 3 + Ipi 1
- Q3W x 4
- Nivo 3
- Q3W x 4
- Nivo 3 + Ipi 1
- Q12W x 8

### Cohort 8
(N = 41)
- Nivo 1 + Ipi 3
- Q3W x 4
- Nivo 3
- Q3W x 4
- Nivo 3
- Q2W x ≤48
Characteristics of Response

On treatment
Off treatment
Ongoing response
First response

Time Since Treatment Initiation (months)

Nivo 0.3 + Ipi 3 (Cohort 1)
Nivo 1 + Ipi 3 (Cohort 2)
Nivo 3 + Ipi 1 (Cohort 2a)
Nivo 3 + Ipi 3 (Cohort 3)
Nivo 1 + Ipi 3 (Cohort 8)
Nivo 1 (Cohort 6)
Nivo 3 (Cohort 7)

Concurrent Therapy
Sequenced Therapy

June 2014 data analysis.
All dose units are mg/kg.

Kluger et al, ESMO 2014
Callahan, Kluger et al, JCO 2018
CA209-067: Study Design (Wolchok et al)

Randomized, double-blind, phase III study to compare NIVO + IPI or NIVO alone to IPI alone

- Unresectable or Metastatic Melanoma
  - Previously untreated
  - 945 patients

Randomize 1:1:1

Stratify by:
- PD-L1 expression*
- BRAF status
- AJCC M stage

N=314

NIVO 1 mg/kg + IPI 3 mg/kg Q3W for 4 doses then NIVO 3 mg/kg Q2W

N=316

NIVO 3 mg/kg Q2W + IPI-matched placebo

N=315

IPI 3 mg/kg Q3W for 4 doses + NIVO-matched placebo

Treat until progression** or unacceptable toxicity

*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.
## Response to Treatment

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>57.6 (52.0–63.2)</td>
<td>43.7 (38.1–49.3)</td>
<td>19.0 (14.9–23.8)</td>
</tr>
<tr>
<td>Two-sided <em>P</em> value vs IPI</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Best overall response — %</strong></td>
<td></td>
<td></td>
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<tr>
<td>Complete response</td>
<td>11.5</td>
<td>8.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Partial response</td>
<td>46.2</td>
<td>34.8</td>
<td>16.8</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13.1</td>
<td>10.8</td>
<td>21.9</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>22.6</td>
<td>37.7</td>
<td>48.9</td>
</tr>
<tr>
<td>Unknown</td>
<td>6.7</td>
<td>7.9</td>
<td>10.2</td>
</tr>
<tr>
<td><strong>Duration of response (months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>NR (13.1, NR)</td>
<td>NR (11.7, NR)</td>
<td>NR (6.9, NR)</td>
</tr>
</tbody>
</table>

*By RECIST v1.1.
NR, not reached.
Unfortunately, NO!!!!
Challenges for Melanoma Researchers

• Cost reduction (drugs cost hundreds of thousands) via improved patient selection - predictive biomarkers needed

• Control of autoimmune toxicities – occur in > 50% of patients treated with ipilimumab+nivolumab

• Patients with autoimmune disorders

• Targeted therapy for the 40% who are WT for both BRAF and NRAS

• Resistance to BRAFi+MEKi combinations has to be overcome

• Outcomes still dismal for uveal melanoma and perhaps less good for mucosal melanomas

• Brain metastasis population needs new approaches

• ~50% of patients do not respond to current immune therapies, and many develop resistance over time – new approaches needed for melanoma that is resistant to PD-1 inhibitors
Studies of other immune therapy combinations for tumors resistant to anti-PD-1 – at Yale and elsewhere

• Combinations with cytokine therapies, e.g. IL2, NKTR 214 (Pegylated IL2), IL-18, IL-12, Interferon alpha and others

• Combinations with adoptive cell therapy regimens

• PD-1 inhibitors + other immune checkpoint modulators, such as LAG-3 inhibitors, TIGIT inhibitors, OX40 agonists and others

• Combinations with targeted therapies and chemotherapy

• Combinations with vaccines

*hundreds of combinations currently in clinical trials
Potential mechanisms of resistance to PD-1 inhibitors

• lack of TIL
• loss of antigen presentation
• T cell exhaustion
• lack of PD-L1 in the tumor or tumor microenvironment
• other immune co-inhibitory molecules on TIL
• Other immune inhibitory cells, such as MDSC, T regs

*sCo-targeting TAMs is the approach currently being studied in our group – αPD-1, αCSF1R and CD40a; collaboration with Kaech and Bosenberg groups
Animal models driven by Braf$^{V600E}$, Pten$^{-/-}$, Cdkn2a$^{-/-}$, YUMM1.7 and YUMM1.7ER, treated with $\alpha$PD-1

Bosenberg et. al
Tumor infiltrating immune cells in GEMM melanoma tumors

Perry et al., J. Experimental Medicine 2018
Combination of CD40a and CSF1Ri vs monotherapy

![Graph showing tumor growth over days post tumor induction for control, CD40, CSF1Ri, and CD40 + CSF1Ri treatments.](image)

Perry et al., Journal of Experimental Medicine, 2018
CD40a + CSF1Ri drives a TAM inflammatory transcriptional program
Effects on T cells

%CD8 T cells of total T cells

PD1 MFI on CD8+ T cells

Control  CD40 agonist  CSF1Ri  CD40 agonist +CSF1Ri

Control  CD40 agonist  CSF1Ri  CD40 agonist +CSF1Ri

- ** p < 0.01
- ns: not significant
Combinations with PD-1 inhibitors

Survival

- Control
- αPD1
- Cd40a
- αCSF1R
- αPD1+CD40a
- αPD1+αCSF1R
- CD40a+ αCSF1R
- Triple

Tumor volume (mm³)

- αPD-1
- CD40a+CSF1Ri
- Triple therapy
RENCA murine kidney cancer model
Bench to bedside

• Collaborations formed with Bristol Myers Squibb and Apexigen

• αPD-1 (nivolumab), αCSF1R (cabiralizumab) and CD40a (APX005M)

• Cabiralizumab and nivo given to hundreds of patients, modest activity in melanoma

• CD40a have significant activity in melanoma, even as single agent, in older trials

• Oligo-site phase I/II trial of APX005M plus nivo in melanoma and lung cancer initiated in 2017
Melanoma patient on nivo+APX005M responding after initial CR to pembrolizumab lasting > 3 years followed by progression pembrolizumab
Phase I/II study of cabiralizumab (αCSF1R) and APX005M (CD40a) with and without nivolumab in patients with melanoma, RCC or NSCLC whose disease progressed on αPD1.

**PHASE I**

- Cohort 1: Cabiralizumab + APX005M 0.03 mg/kg
- Cohort 2: Cabiralizumab + APX005M 0.03 mg/kg + nivolumab 240 mg
- Cohort 3: Cabiralizumab + APX005M 0.1 mg/kg
- Cohort 4: Cabiralizumab + APX005M 0.1 mg/kg + nivolumab 240 mg
- Cohort 5: Cabiralizumab + APX005M 0.3 mg/kg
- Cohort 6: Cabiralizumab + APX005M 0.3 mg/kg + nivolumab 240 mg

**PHASE II**

First stage: 13 patients treated with Cabiralizumab, Nivolumab and APX005M i.v. q3w

- ≤ 1 responders: Stop study
- ≥ 1 responders: Enroll 21 additional patients, 2nd stage

Primary objective: response rate and safety
Secondary objective: Progression free and overall survival
Exploratory biomarker end points

*Identical study design for RCC and NSCLC*

Pis: Harriet Kluger, Sarah Weiss
Blood collection and baseline imaging → Cycle 1

Blood collection → Cycle 2

Blood collection → Cycle 3

Blood collection → Cycle 4

Treatment: Every 3 weeks

Weeks 0 1 2 3 4 5 6 7 8 9 10

Response evaluation:
MRI brain + CT chest/abdomen/pelvis OR PET-CT every 4 cycles

Progression of disease

Blood collection → Cycle x

Pre-treatment biopsy → Mandatory biopsy
Phase I Updates

• Cohorts 1, 2 and 3 have been filled. Two patients with melanoma, 7 with RCC.

• Overall toxicities: peri-orbital edema, elevated CPK, AST and ALT, fevers and signs of cytokine release in first 48 hours

• Recommended phase II dose still to be determined

• Early flow cytometry studies (with Meffre lab), pre- and post-treatment:
  - changes in B cells, NK cells and monocytes in the circulation
  - increase in FAS expression on B cells
  - increase in HLA DR expression on monocytes
  - no change in T cell number, but increase in central memory T cells (CD45RO)
  - decrease in T regs, including Helios positive T regs
  - increase in proliferating T cells (Ki67 on CD4 positive cells)
Conclusions

• Despite progress in treating advanced melanoma, particularly with anti-PD1, not all patients respond.

• Multiple mechanisms of resistance described, including abundance of tumor associated macrophages and a paucity of T cell infiltration. These might be harnessed to develop new regimens for melanomas resistant to anti-PD-1.

• Co-targeting the innate and adaptive immune system with CSF1R inhibitor + CD40 agonist results in better anti-tumor activity than either alone and increases CD8 tumor content in animals.

• Treatment of mice bearing anti-PD-1 resistant tumors with these drugs in combination with nivolumab appears superior to all doublets, including αCSF1R+CD40a.

• Findings confirmed in Renca model, although the percent of mice with tumor rejection is lower, consistent with picture seen in humans.

• A clinical trial testing this finding has been initiated for patients with melanoma, renal cell carcinoma and non-small cell lung cancer.
Acknowledgements

• Yale lab collaborators: Susan Kaech, Marcus Bosenberg, Eric Meffre, Lucia Jilaveanu, William Damsky
• Lab members: Curtis Perry, Irina Krykbaeva, Christopher Zito, Lin Zhang
• Clinical collaborators: Mario Sznol, Sarah Weiss, Scott Gettinger, Roy Herbst, Michael Hurwitz
• Clinical research team: Neta Levitt, Amanda Ralabate
• Pharmaceutical collaborators: Serena Perna (BMS), Ovid Trifan (Apexigen)
• Funding for pre-clinical work: Yale SPORE in Skin Cancer, NIH K24, NIH K12, Yale Cancer Center