The Challenge of Bringing Forward New Agents for Systemic Therapy of Melanoma

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Melanoma in 2008

- Epidemic Proportions of Disease
- Primary/Regional Prognostic Assessment
- Advanced/Distant Metastatic Disease
  - New Chemotherapy, Cytokine, Antibody & Vaccine Options
  - Relevance of Immunobiology to Disease/Response:
    - Cytokines and Immunoregulation
    - Tumor Antigens & Vaccines
    - Dendritic Cells, T cells,
    - Immunostimulatory and Disinhibitory Antibodies
### Incidence and Prognosis

- **59,940 New cases of melanoma of the skin in 2007**
  - ~8110 Deaths
  - 4% of new skin cancers
  - Majority of skin cancer deaths

### Disease Stage vs. 5-Yr Survival

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>5-Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>95%</td>
</tr>
<tr>
<td>Regional</td>
<td>65%</td>
</tr>
<tr>
<td>Distant</td>
<td>15%</td>
</tr>
</tbody>
</table>

Changes in Overall Cancer Mortality (1975-2003), United States

- Melanoma
- Prostate Cancer
- Breast Cancer
- Colorectal Cancer
- Cervical Cancer

SEER Cancer Registry, 2003
Which primary melanomas will be lethal?
The Initial Forum: Stage IV Melanoma

- **M1a**
  - Defined by site in skin/soft tissue/nodes without elevation of LDH

- **M1b**
  - Defined by site in skin/ST/N and/or lung without elevation of LDH

- **M1c**
  - Defined by visceral site of involvement beyond lung or other distant site with elevation of LDH

(Usefully applied for multiple clinical trials)
Systemic Therapy of Advanced Melanoma

Stage IV (inoperable) survival <5% at 5+ years

- Only one approved cytotoxic agent in use
  - Dacarbazine (Temozolomide) with 6.8-12% response in modern trials, rarely durable

- Only one (biological) agent approved in modern times
  - High-dose IL-2, with 15% response and 5% durable responses
High Dose IL-2 Therapy Approved 1998

- RR: 16% (43 / 270)
- Durable responses in 6%
  - Median Duration 8.9 mos
  - CR: not reached

(N=270, collected phase II studies) Atkins et al., JCO 1999
Interleukin-2 Summary

- High-dose bolus IL-2 approved by FDA in 1998
- Response rate ~16% of which 5-6% are durable remissions
- Toxicity and supportive care an issue
- Low dose IL-2 is not as effective
- Uncertain that any new agent with similar impact would receive approval
Cooperative Group Meta-analysis of 70 Phase II Trials, 2100 Patients, 35 Years

Benchmarks for OS and PFS Endpoints

**Survival at 1 year 30%**

**Progression Free Survival at 1 year 18%**

**One year OS** → 25%

**Six month PFS** → 15%

**Numbers of patients** →

---

**A**

**B**

---

**Trial-Arm Sample Size**

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**One year OS** → 25%

**Six month PFS** → 15%
E3695: Survival Data

$$p = 0.696$$
Why so little impact of chemotherapy and combinations to date upon melanoma?

• Tumor cell drug resistance:
  – Mismatch Repair
  – AlkI guanine alkyl transferase (AGAT)
  – Base Excision Repair
• Specific molecular mechanisms of progression
  – BRAF mutated in 70% of melanoma
  – STAT3 constitutively activated in melanoma
• Tumor cell resistance to apoptosis
  – BCL2
  – Survivin
Summary

• No combination of agents is yet better than the single agent dacarbazine
• HD IL-2 produces long-term remissions in 5-10% of patients (very selected)
• Randomized multi-center phase III trials to date have all failed to reach primary endpoints with significant differences
Active stage IV melanoma is associated with immunological tolerance and Th2-type rather than effective Th1-type immune responses to MAGE-A6 & EphA2

*AD = Active Disease; NED = No evidence of Disease.
Patients exhibited Th1-type immunity to Flu/EBV Th Epitopes
Adjuvant Trials have given more unequivocal results

• Vaccines, Adoptive Cellular/Passive Ab Transfer
  – Crude whole cell vaccines (Canvaxin)
  – Antibody (B cell)-inducing Gangliosides (GMK)
  – Effector T cell-inducing peptides (E1696; E4697; E1602); proteins, DNA

• Interferons & Cytokines
  – IFN-γ (E4687, S8710)
  – IL-2 (S0008)
  – GM-CSF [peptide vaccines] (E4697)
  – IFNα2—the single agent established in current standard practice through mature phase III randomized controlled multicenter cooperative group investigations

Key: statistically significant negative impact in Phase III Trial; Trial results pending; ph II or III evidence of significant benefit
MMAIT: Phase III Trial of Allogeneic Melanoma Vaccine in Resected, Metastatic Melanoma

**Stage III/IV melanoma; no evidence of disease following resection**

<table>
<thead>
<tr>
<th></th>
<th>Stage III</th>
<th></th>
<th>Stage IV</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine</td>
<td>Placebo</td>
<td>$P$</td>
<td>Vaccine</td>
</tr>
<tr>
<td>DFS</td>
<td>43 mo</td>
<td>&gt;60 mo</td>
<td>0.047</td>
<td>8.3 mo</td>
</tr>
<tr>
<td>5-Yr DFS</td>
<td>47%</td>
<td>52%</td>
<td></td>
<td>27%</td>
</tr>
<tr>
<td>OS</td>
<td>&gt;69 mo</td>
<td>&gt;69 mo</td>
<td>0.04</td>
<td>32 mo</td>
</tr>
<tr>
<td>5-Yr OS</td>
<td>59%</td>
<td>68%</td>
<td></td>
<td>40%</td>
</tr>
</tbody>
</table>

BCG=Bacille Calmette-Guérin; DFS=disease-free survival.

Morton. ASCO. 2007 (abstr 8508).
MMAIT: Results

MMAIT-IV

DFS (%)

Time (Months)

BCG + Vaccine

BCG + Placebo

MMAIT-III

DFS (%)

Time (Months)

BCG + Placebo

BCG + Vaccine

OS (%)

Time (Months)

BCG + Placebo

BCG + Vaccine

Morton. ASCO. 2007 (abstr 8508).
Established and New Potential Adjuvant Immunotherapy For Melanoma

- IFNs augment effector cell numbers and function, repolarizing the response to tumor cells.
- IFNs also inhibit proliferation and induce melanization in melanoma.
Mature Phase III Trials of Adjuvant HDI for Stage IIB-III Melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization</th>
<th>Induction</th>
<th>Maintenance</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1684</td>
<td>Surgery</td>
<td>IFN-α2b</td>
<td>48 wks</td>
<td>52 wks</td>
</tr>
<tr>
<td></td>
<td>Randomized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=280)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(within 56 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E1690</td>
<td>Surgery</td>
<td>IFN-α2b</td>
<td>48 wks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Randomized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=608)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(within 70 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E1694</td>
<td>Surgery</td>
<td>IFN-α2b</td>
<td>48 wks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Randomized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=774)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HDI=high-dose interferon.

E1684, E1690, and E1694: Durable Impact upon RFS* and Significant Impact on OS**

E1684: IFN vs Observation**

HR = 1.38  
P_2 = 0.02

E1690: IFN vs Observation*

HR = 1.24  
P_2 = 0.09

E1694: IFN vs GMK**

HR = 1.33  
P_2 = 0.006

RFS = relapse-free survival.

Overall survival benefit for pivotal E1684 to >10 years is confirmed by E1694

E1684

IFN vs Observation: $p_2 = 0.18$, $p_1 = 0.09$, HR = 1.22

E1690

IFN vs Observation: $p_2 = 0.98$, HR = 1.00

E1694

IFN vs GMK: $p_2 = 0.04$, HR = 1.32

Issues with high-dose IFNα survival benefits

• Two independent trials demonstrate significant durable survival benefits of IFNα
  – But a third does not: change in entry requirement of lymphadenectomy and asymmetric crossover after FDA approval of HDI provides a plausible explanation
• Benefit upon overall survival and relapse-free survival are not parallel after 10 yrs
  – Non-melanoma causes of death at >10 yrs may erode survival differences (EORTC 18952 ↑cardiac deaths?)
  → Need analysis of death causes, salvage patterns
• Cost/Toxicity
  – >90% of E1694 patients without relapse completed 1 year of therapy, and cost efficacy is ~ other accepted therapies
E18952 and E18991: Results

**E18952**

- **DMFS**
  - Observation (165 observed events)
  - 13-month IFN-α (316 observed events)
  - 25-month IFN-α (296 observed events)

**E18991**

- **DMFS (ITT)**
  - Peg-IFN-α2b
  - Observation

### Adjuvant IFN Therapy: Tolerability and Treatment Duration

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Endpoint</th>
<th>Patients Remaining on IFN Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1684</td>
<td>20 MU/m²/day 1 mo, then 10 MU/m² 3/wk 48 wks</td>
<td>6.9 yrs</td>
<td>~60% Received ≥80% of target dose</td>
</tr>
<tr>
<td>E1690</td>
<td>20 MU/m²/day 5/wk 1 mo, then 10 MU/m² 3/wk 48 wks</td>
<td>4.3 yrs</td>
<td>59% Required dose delay or reduction</td>
</tr>
<tr>
<td>E1694</td>
<td>20 MU/m²/day 5/wk 1 mo, then 10 MU/m² 3/wk 48 wks</td>
<td>16 mo</td>
<td>90%</td>
</tr>
<tr>
<td>E18952</td>
<td>10 MU 5/wk 4 wks, then 10 MU 3/wk</td>
<td>13 mo</td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td>10 MU 5/wk 4 wks, then 5 MU 3/wk</td>
<td>25 mo</td>
<td>80%</td>
</tr>
<tr>
<td>E18991</td>
<td>6 μg/kg/wk 8 wks, then 3 μg/kg/wk</td>
<td>5 yrs</td>
<td>30%</td>
</tr>
<tr>
<td>WHO 16</td>
<td>3 MU 3/wk</td>
<td>3 yrs</td>
<td>100%</td>
</tr>
<tr>
<td>French Group</td>
<td>3 MU 3/wk</td>
<td>18 mo</td>
<td>65%</td>
</tr>
</tbody>
</table>
How to improve the therapeutic index?

→ Dissect the roles of induction vs. maintenance

• All positive trials of IFNα utilized IV induction at 20MU/m² ($C_{\text{max}} > 10,000\text{u/ml}$)

• Is one month of IV IFNα2b both necessary and sufficient?
  – Intergroup E1697
Hypothesis: Induction IV IFN is necessary and sufficient to achieve durable adjuvant benefit in intermediate-risk melanoma patients

<table>
<thead>
<tr>
<th>STRATIFICATION</th>
<th>R A N D O M I Z E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic Lymph Node Status</td>
<td>Arm A: Observation</td>
</tr>
<tr>
<td>Known</td>
<td>Arm B: 4 week high-dose IFN alfa-2b (Intron A)</td>
</tr>
<tr>
<td>Unknown</td>
<td>20 MU/m²/d qd IV for 5 consecutive days out of 7 (M-F) every week times 4 weeks</td>
</tr>
<tr>
<td><strong>Lymph Node Staging Procedure</strong></td>
<td></td>
</tr>
<tr>
<td>Sentinel Lymph Node Procedure</td>
<td></td>
</tr>
<tr>
<td>Elective Lymph Node Dissection</td>
<td></td>
</tr>
<tr>
<td>No Lymphadenectomy</td>
<td></td>
</tr>
<tr>
<td>Breslow Depth</td>
<td></td>
</tr>
<tr>
<td>1.5 - 3 mm</td>
<td></td>
</tr>
<tr>
<td>3.1 - 4 mm</td>
<td></td>
</tr>
<tr>
<td>&gt; 4 mm</td>
<td></td>
</tr>
<tr>
<td>Ulceration of Primary Lesion</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Disease Stage</td>
<td></td>
</tr>
<tr>
<td>Lymph Node Positive</td>
<td></td>
</tr>
<tr>
<td>Lymph Node Negative</td>
<td></td>
</tr>
</tbody>
</table>
Gaps in Therapy of Melanoma

• More precise markers of prognosis
  – Treat only those at risk of relapse

• Markers to predict treatment benefit
  – Treat only those capable of response
  • Anti-tumor immunity
  • Autoimmunity to pigment cell markers, other tissue antigens
Neoadjuvant Therapy in Patients with Stage III Melanoma
UPCI 00-008

• Biomarker discovery to better predict treatment efficacy
• Define molecular mechanisms of treatment
  – Which of the multiple known actions are critical?
  – Direct pro-apoptotic, anti-angiogenic, or indirect immunomodulatory effects?
• Clinical response assessment at 4 weeks for correlation with RFS and OS
Stage IIIB, IIIC melanoma (Tx, N2b, or N3, M0)

IFN-α2b induction therapy (20 MU/m²/d IV 5d/wk, × 4 wks)

IFN maintenance therapy (10 MU/m²/d tiw, × 48 wks)

Enrollment

Excisional biopsy (sample 1)

Radical regional lymphadenectomy (sample 2)

UPCI 00-008 Schema

Moschos et al., 2006
Results

• 20 patients enrolled
  – (age median 59, range 40-78; 13 males)
• 11 with recurrent disease
  – 15 completed 4 weeks of HDI
• Objective Response at 4 weeks of treatment:
  
  Clinical
  1 complete, 10 partial
  
  Pathologic
  3 complete, 2 microscopic residual disease

Moschos et al., 2006
HDI increases the number of immunologically relevant cells infiltrating regional lymph node metastatic tumor

**CD3**
- CD3+ responders
- CD3+ nonresponders

**CD4**
- CD4+ responders
- CD4+ nonresponders

**CD11c**
- CD11c+ responders
- CD11c+ nonresponders

**CD83**
- CD83+ responders
- CD83+ nonresponders

**CD56**
- CD56+ responders
- CD56+ nonresponders

**CD86**
- CD86+ responders
- CD86+ nonresponders

- $p=0.09$
- $p=0.14$
- $p=0.06$
- $p=0.14$
- $p=0.09$
- $p=0.50$
HDI Down-Regulates pSTAT3 Tyr705 And STAT3 Expression in Tumor Cells

Wang et al., Clin Cancer Res 2007
HDI Down-Regulates pSTAT3 Tyr705 and STAT3 in Regional Lymph Node Metastases of Melanoma

![Graph showing the down-regulation of pSTAT3 and STAT3 with statistical significance.]

- pSTAT3: $P = .002$
- STAT3: $P = .028$

$n = 7$

Wang et al., Clin Cancer Res 2007
HDI Up-regulates pSTAT1 Tyr701 and Down-regulates pSTAT3 Tyr705 in Melanoma

Wang et al., Clin Cancer Res 2007
Conclusions from Neoadjuvant High-Dose IFN-α2b Trial 00-008

• Clinical response at day 29 is improved
  – 55% of patients with objective response
  – Radiographic and pathologic criteria
  – Relapse-free and overall survival data too early for final assessment

• Molecular and immunologic effects:
  – ↓ pSTAT3/STAT3, IFNAR2
  – ↑ pSTAT1, pSTAT1/3 ratio, and TAP2
  – ↑ CD3 T cell and CD11c dendritic cell populations in tumor
Autoimmunity as a Key to Therapeutic Role of IL-2, IFN-α, and Anti-CTLA4 Antibodies
Prognostic Significance of Autoimmunity

- Subset analysis of phase III trial
- 200 Patients with stage IIB/IIIC melanoma

Arm 1: IFN-α2b 15 MU/m² 5 x weekly for 4 wks, then observation (N=96)

Arm 2: Same as Arm 1 + IFN-2b 10 MU 3 x weekly for 48 wks (N=104)

<table>
<thead>
<tr>
<th>Manifestation of Autoimmunity</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear Antibodies</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Anticardiolipin Antibodies</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Clinical Manifestations</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Multiple Manifestations</td>
<td>16</td>
<td>8</td>
</tr>
</tbody>
</table>

Multivariate Analysis for OS in High-Risk Melanoma Patients Receiving HDI

<table>
<thead>
<tr>
<th>Positive Autoimmunity Status</th>
<th>RFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>At 3 mo</td>
<td>0.15 (0.06-0.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>0.08 (0.03-0.22)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Time to Progression**

- Patients with autoimmunity (N=52)
- Patients without autoimmunity (N=148)

**OS**

- Patients with autoimmunity (N=52)
- Patients without autoimmunity (N=148)

HDI=high-dose IFN-α2b.

Autoimmunity Is Correlated With Improved Outcomes in Melanoma

- Development of vitiligo, thyroiditis, and autoantibodies to other endocrine targets predicts reduced relapse risk and improved DFS and OS
  - Results confirmed in subset analyses of 13A/98 (phase III), E1694 (phase II), and E2696 (phase II)
- Induction of autoimmunity is a common thread for active immunomodulatory therapies of this disease
  - Spontaneous vitiligo is a favorable attribute
    - For disease outcome
    - For response to therapy: IL-2; anti–CTLA-4; IFN
- **Autoimmunity to endocrine and pigment cell targets is a surrogate for immunity to tumor antigens yet to be defined**

Biomarkers of Disease Progression

• Blood LDH: reanalysis of GM301 and E18951
  – Trials had identical eligibility
  – Higher LDH correlated with decreased OS in advanced melanoma
  – Elevations predictive of nonresponse to oblimersen treatment
    • Patients with nonelevated baseline LDH had higher OS (12.3 mo vs 9.9 mo; \( P=0.0009 \)) and ORR (20.8% vs 7.2%; \( P=0.002 \)) in oblimersen + DTIC arm vs DTIC arm

• S100
  – \( S100 \geq 0.08 \mu g/L \) is an independent prognostic marker for RFS and OS
  – \( S100B \) is a prognostic marker for DMFS in patients with stage III melanoma

Keilholz. ASCO. 2007 (abstr 8552); Stuckert. ASCO. 2007 (abstr 8506); Suciu. ASCO. 2007 (abstr 8518).
Multiplexed Analysis of Serum Biomarkers

- High-throughput xMAP multiplex immunobead assay
  - Tested 29 analytes: cytokines, chemokines, angiogenic factors, growth factors, and soluble receptors
  - Serum of 378 matched healthy subjects vs 179 patients with melanoma from ECOG E1694
    - Phase III trial of HDI vs ganglioside vaccine in resected, high-risk, cutaneous melanoma

- Serum concentrations of many markers were found to be higher in patients with resected, high-risk melanoma than in healthy individuals

Predictive Role of Pretherapy Serum Cytokine Levels for IFN Adjuvant Therapy

Patients Receiving HDI

![Bar charts showing IL-1β, IL-6, and TNF-α levels for different RFS categories (RFS<1, RFS 1-5, RFS >5) for patients receiving HDI. The asterisk (*) indicates statistical significance.]

Patients Receiving GMK

![Bar charts showing IL-1β, IL-6, and TNF-α levels for different RFS categories (RFS<1, RFS 1-5, RFS >5) for patients receiving GMK. The asterisk (*) indicates statistical significance.]

Conclusions

- IL-2, IFNα, and anti CTLA4 blocking antibodies induce durable remission in metastatic disease through mechanisms that appear to be immunological, and variably associated with induction of autoimmunity to normal tissues.

- Adjuvant arena may be the most informative for new biological agents.
CTLA-4

- Glycoprotein expressed on the surface of activated T cells
- Downregulates T-cell response
  - Decrease in IL-2 production
  - Arrest of cell cycle progression
- Anti-CTLA-4 monoclonal antibody antitumor activity in murine models
Anti-CTLA4 Blocking Antibodies

- Potent new inducer of autoimmunity associated with durable antitumor effects in advanced melanoma

- Potentially greater impact in adjuvant setting vs. microscopic disease?
## CTLA-4 Antagonistic mAbs in Clinical Development

<table>
<thead>
<tr>
<th>Antibody Name</th>
<th>Former Names</th>
<th>Type of Antibody</th>
<th>Ig Subtype</th>
<th>Plasma Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>MDX010 BMS-734,016</td>
<td>Fully human</td>
<td>IgG1</td>
<td>12-14 days</td>
</tr>
<tr>
<td>Tremelimumab</td>
<td>CP-675,206 ticilimumab</td>
<td>Fully human</td>
<td>IgG2</td>
<td>22 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody-dependent</td>
<td>+++</td>
<td>±</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Cellular Cytotoxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complement Fixation</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>–</td>
</tr>
<tr>
<td>Plasma Half-life</td>
<td>23 days</td>
<td>23 days</td>
<td>9 days</td>
<td>23 days</td>
</tr>
</tbody>
</table>

## Published Full Text Manuscripts of Antitumor Activity of Anti–CTLA-4 mAb in Melanoma

<table>
<thead>
<tr>
<th></th>
<th>Antibody</th>
<th>Combination</th>
<th>mAb Dose</th>
<th>Dose</th>
<th>Patients With Measurable Melanoma</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodi, 2003</td>
<td>Ipilimumab (MDX010)</td>
<td>No</td>
<td>3 mg/kg</td>
<td>Single</td>
<td>7</td>
<td>0%</td>
</tr>
<tr>
<td>Attia, 2005</td>
<td>Ipilimumab (MDX010)</td>
<td>gp100 peptides</td>
<td>3 mg/kg</td>
<td>q3w</td>
<td>56</td>
<td>7%</td>
</tr>
<tr>
<td>Phan, 2003</td>
<td>Ipilimumab (MDX010)</td>
<td>HD IL-2</td>
<td>0.1-3 mg/kg</td>
<td>q3w</td>
<td>36</td>
<td>8%</td>
</tr>
<tr>
<td>Maker, 2005</td>
<td>Ipilimumab (MDX010)</td>
<td>No</td>
<td>3-9 mg/kg</td>
<td>q3w</td>
<td>46</td>
<td>5%</td>
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<tr>
<td>Maker, 2006</td>
<td>Ipilimumab (MDX010)</td>
<td>No</td>
<td>3-9 mg/kg</td>
<td>q3w</td>
<td>46</td>
<td>5%</td>
</tr>
<tr>
<td>Ribas, 2005</td>
<td>Tremelimumab (CP-675,206)</td>
<td>No</td>
<td>0.01-15 mg/kg</td>
<td>Single</td>
<td>29</td>
<td>4%</td>
</tr>
<tr>
<td>Reuben, 2006</td>
<td>Tremelimumab (CP-675,206)</td>
<td>No</td>
<td>10-15 mg/kg</td>
<td>q1m or q3m</td>
<td>30</td>
<td>5%</td>
</tr>
</tbody>
</table>

Phase I/II Trial: Tremelimumumab in Stage III/IV Melanoma

Stage III/IV melanoma

Arm 1: CP-675,206 10 mg/kg monthly (N=20)

Arm 2: CP-675,206 15 mg/kg every 3 mo (N=10)

<table>
<thead>
<tr>
<th>Response</th>
<th>IRAE+</th>
<th>IRAE–</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>ATR</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Adverse Events

<table>
<thead>
<tr>
<th>IRAE</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>15 mg/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- IRAE+/ATR+ correlation between CTLA-4 and glucocorticoid-induced TRFR transcripts ($P=0.015$)
- IRAE–/ATR– PD1 receptor ($P=0.000$)

ATR=antitumor response; IRAE=immune-related adverse event.

Phase I/II Trial: Tremelimumab in Stage III/IV Melanoma (Cont.)

Phase I

Cohort 1:
Tremelimumab 3 mg/kg monthly ≤12 mo (N=3)

Cohort 2:
Tremelimumab 6 mg/kg monthly ≤12 mo (N=3)

Cohort 3:
Tremelimumab 10 mg/kg monthly ≤12 mo (N=8)

Phase II

Arm 1:
Tremelimumab 10 mg/kg monthly (N=44)

Up to 1 Year

Arm 2:
Tremelimumab 15 mg/kg every 3 mo (N=46)

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Phase I</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg/kg monthly</td>
<td>10 mg/kg monthly</td>
<td>15 mg/kg every 3 mo</td>
</tr>
<tr>
<td>6 mg/kg monthly</td>
<td>10 mg/kg monthly</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg monthly</td>
<td>10.2 mo</td>
<td></td>
</tr>
<tr>
<td>22.7 mo</td>
<td>11.5 mo</td>
<td></td>
</tr>
</tbody>
</table>

OS

<table>
<thead>
<tr>
<th></th>
<th>8 mo</th>
<th>6 mo</th>
<th>22.7 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>58%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1-Yr OS

<table>
<thead>
<tr>
<th></th>
<th>32%</th>
<th>46%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Yr OS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Phase II Trial: Tremelimumumab in Advanced Melanoma**

**Stage I**
- **Randomized**
  - Arm 1: Tremelimumab 10 mg/kg monthly (N=18)
  - Arm 2: Tremelimumab 15 mg/kg every 3 mo (N=18)

**Stage II**
- **Nonrandomized**
  - If 3 objective responses, proceed to stage II
  - Arm 1: Tremelimumab 10 mg/kg monthly (N=26)
  - Arm 2: Tremelimumab 15 mg/kg every 3 mo (N=28)

**Toxicities***

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Diarrhea/Colitis</td>
<td>25%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Pancreatitis/Lipase</td>
<td>2.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>2.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Skin Rash</td>
<td>2.5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Ribas. ASCO. 2007 (abstr 3000). *Toxicity increases with continued dosing.
Phase I/II Trial: Ipilimumab in Patients With Unresectable Stage III/IV Melanoma

Unresectable metastatic melanoma

A: Ipilimumab 2.8, 3, or 5 mg/kg
   Days 1, 57, and 85 (N=34)

B: Ipilimumab 7.5, 10, 15, or 20 mg/kg
   Single doses (N=30)

C: Ipilimumab 10 mg/kg every 3 wks
   Days 1, 22, 43, and 64 (N=24)
### Phase I/II Trial: Ipilimumab in Patients With Unresectable Stage III/IV Melanoma

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Response</th>
<th>Duration</th>
<th>Disease Control Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (N=34)</td>
<td>ORR 1 PR</td>
<td>246 days</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>SD 4</td>
<td>29, 61, 168, 172 days</td>
<td></td>
</tr>
<tr>
<td>B (N=30)</td>
<td>ORR 1 CR</td>
<td>211 days</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>SD 3</td>
<td>37, 109, 395 days</td>
<td></td>
</tr>
<tr>
<td>C (N=23)</td>
<td>ORR 1 CR, 1 PR</td>
<td>263, 275 days</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td>SD 7</td>
<td>99, 190, 194, 194, 246, 351, 379 days</td>
<td></td>
</tr>
</tbody>
</table>

Phase I/II Trial: Ipilimumumab in Patients With Unresectable Stage III/IV Melanoma: Results

- **IRAE**
  - Overall incidence: 72%
  - All patients with ORR and 13/14 SD had IRAE
  - Most events grade 1/2 and reversible

- **25 Patients had SAEs**

- **9 Patients across all doses had ipilimumab-related SAEs**
  - 1 Patient perforated bowel @ 2 doses of ipilimumab 10 mg/kg

- **Ipilimumab-related SAEs**
  - Diarrhea, colitis, nausea, cerebral edema, gastrointestinal perforation, and abdominal pain

Proposed US Intergroup E1607 Phase III trial: Anti-CTLA4 Antibody CP-675,206 vs. Placebo

Patients with T (any) N2 post IFN -or- any resectable M1a or M1b

Primary endpoints: Survival, progression-free interval
Secondary Analyses: Autoimmune, antitumor responses
Building the Next Generation Adjuvant Therapy

• Anti-CTLA4 for IFN failures in stage IIIB
  – Intergroup ECOG-SWOG study E1607(Tremelimumab 15mg/kg q3mos) is in planning;
  – EORTC study of MDX-010 10 mg/kg q 3 wks is in planning
• Combinations of IFNα and other agents
  – Vaccines→Recall and polarize response w/IFN (04-125)
  – Cytotoxic Antibodies→Improve ADCC with IFN (07-023)
  – Anti-CTLA4: Tremelimumab combined w/IFN (05-125)
• Neoadjuvant studies may afford a rapid avenue to evaluate therapeutic efficacy and mechanism of candidate agents & combinations
Opportunities

- Evaluate more specific anti-tumor immune responses induced by established and investigational agents
  (IL-2, IFNα, anti-CTLA4 blocking antibodies)
- Identify genetic determinants of capacity to induce effective antitumor immunity
- Define specific prognostic and predictive markers of immunity in conjunction with ongoing/new trials of immunomodulators