Melanoma: Adjuvant Therapy and Emerging Treatments for Metastatic Disease.

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Case Presentation

AJCC: Survival by Stage

American Joint Commission on Cancer; 7th Edition.

AJCC: Survival Stage I-II

Adjuvant Therapy: High Risk Disease

Adjuvant Therapy

- High Risk Patients: Stage II/III
  - Deeply Invasive
  - Node +
  - High Mitotic Rate
  - Ulcerated Primaries

- Interferon Only FDA approved RX (1996)
**Adjuvant Interferon: E1684**
- 267 patients
- Stage IIB/III
- High Dose INF Induction/Maintenance vs Observation
- Results
  - 5yr RFS 37% vs 26%
  - Median OS 3.8 vs 2.8yrs
  - 5yr OS 46% vs 37%
- Led to 1996 fast track FDA approval
- OS benefit lost on subsequent analysis

**Adjuvant Interferon: E1690**
- 642 patients
- Stage IIB/III
- HDI Induction/Maintenance vs LDI vs Observation
- Results
  - 5yr RFS 44% vs 40% vs 35%
  - 5yr OS 52% vs 53% vs 55%

**Adjuvant Interferon: ECOG Pooled Analysis E1684/E1690**
- 713 patients
- HDI Induction/Maintenance vs Observation

**Pegylated Interferon: EORTC 18991**
- 1256 patients
- Stage III
- Pegylated INF X 5yrs vs observation
- Results
  - Median RFS 35 vs 26 mos
  - No OS difference
- FDA approved March 2011

**Meta-analysis: JNCI 2010**
- 14 randomized controlled trials
- 12 trials with INF vs Observation
- 8122 patients
- 4362 patients received INF
- Disease free and overall survival both statistically significant.
**Adjuvant Interferon**

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<th>LC</th>
<th>UC</th>
<th>Patients</th>
<th>Events</th>
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**Interferon Toxicity: E1690**

- Dose delays or reductions in almost 60% of patients in both induction and maintenance
- Grade 3/4
  - Neutropenia 44%
  - Liver toxicity 29%
  - Fatigue 24%
  - Neuroclinical 20%
  - Myalgia 17%

**Conclusions: Adjuvant Therapy**

- INF only FDA approved adjuvant RX
- RFS benefit consistent
- OS benefit debated
- Most effective dose/schedule unclear
  - Standard vs pegylated
  - 4 weeks vs 12 months vs longer
- Toxic/Poorly Tolerated
- NCCN lists observation, trial, and INF as equal options in high risk setting

**Case Presentation**

- 81 y/o male
- Dx Anal Melanoma Jan-2009
- Primary Therapy APR
- 2 + Nodes
- Adjuvant GM-CSF
- Relapse/Metastatic Disease < 1 year
- Multiple metastatic pulmonary nodules
- SWOG 0826: CDKI X 6 mos
- Second Line Therapy: Ipilimumab

**Ipilimumab**

May 2010 - March 2011
**Ipilimumab**

- **TARGET:** Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)
  - Check point/down regulates T-cell activation
  - Harnesses the immune response
- **Ipilimumab:** Fully human monoclonal antibody, blocks CTLA-4
- **Mechanism:**
  - Augmented T-cell activation
  - T-cell mediated anti-tumor response
- "Unleashes the immune system", “takes off the breaks”.

**Study Overview**

- **676 patients**
  - Stage 3 unresectable or stage IV
  - Progression on first line therapy
- **Three Treatment Arms**
  - Ipilimumab + gp100 peptide vaccine
  - Ipilimumab alone
  - GP100 alone
- **Treatment Schedule:** IV infusion Q3 weeks X 4 doses.

**Results**

<table>
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<tr>
<th>Treatment Arm</th>
<th>Response Rate</th>
<th>Disease Control</th>
<th>Overall Survival</th>
<th>2yr Survival</th>
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<tbody>
<tr>
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<td>20%</td>
<td>10 mos</td>
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<tr>
<td>Ipiilimumab</td>
<td>11%</td>
<td>29%</td>
<td>10 mos</td>
<td>24%</td>
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<tr>
<td>GP100</td>
<td>2%</td>
<td>11%</td>
<td>6.4 mos</td>
<td>14%</td>
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</table>

**Results Continued**

- **Durable responses**
  - 60% maintained response at 2 years in Ipilimumab alone arm.
- **Delayed responses seen**
- **Responses seen with re-induction**

**Original Article**

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robson, M.D., Ph.D., Dirk Schadendorf, M.D., Veronique C. Hassel, M.D., Waltraud Averley, M.D., Moritz J. van den Elsenbergh, M.D., Ph.D., Jose Lutzky, M.D., Paul Longin, M.D., Julio M. Avedo, M.D., Gerald P. Lintell, M.S., Ph.D., David Hogg, M.D., Christian H. Ottenhauser, M.D., Ph.D., Gesine Lebbe, M.D., Christian Paschke, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jeddi D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Than, Ph.D., Michael J. Volin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

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**Ipilimumab Toxicity**

- Immune related toxicity in 60%
- Grade 3 or 4 in 10-15% patients
- Common toxicities
  - Diarrhea
  - Rash
  - Endocrine
  - Hepatitis
  - Neuropathy
- Prompt corticosteroids important.
- 12 deaths in Ipilimumab arms vs 2 in GP100

**BRAF Inhibitors**

- B-RAF:
  - Serine-threonine protein kinase
  - Cell signaling via MAP kinase pathway
- BRAF mutations 40-60% melanomas
  - 90% V600E mutation
  - Constitutively activates BRAF and downstream signaling
- PLX4032 potent oral BRAF inhibitor

**Summary**

- Adjuvant benefit of Interferon is modest with questionable improvement in OS.
- Ipilimumab first therapy for advanced melanoma showing OS benefit in phase III trial
- BRAF agents on the horizon
- Ipilimumab in adjuvant setting?? Trials pending.