A phase III, randomized, double-blind, multicenter study comparing monotherapy with ipilimumab or gp100 peptide vaccine and the combination in patients with previously treated, unresectable stage III or IV melanoma

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Background

- Advanced melanoma (Stage III/IV) has an increasing global incidence. Many patients are diagnosed at a relatively young age, and the disease carries a poor prognosis.
- Despite multiple trials of experimental therapeutics, there are few good therapeutic options for patients with advanced melanoma.
  - There has been no documented improvement in survival for these patients in over 30 years.
  - There have been no new FDA approved drugs since IL-2 was approved over 10 years ago,
  - A meta-analysis of 70 cooperative group Phase II trials to establish baseline overall survival (OS) curves for these patients revealed that every one of these studies was negative (Korn, JCO, 2008)
  - First line therapy is roughly equivalent to best supportive care.
- As a result, immunotherapy for melanoma has been under active investigation.
- The HLA-A2-restricted, gp100 peptide induces a specific T-cell immune response in melanoma, and has been tested in combination with high-dose IL-2 (Sosman, JCO, 2008).
  - It enhances clinical activity when combined with other immunotherapy.
- Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is up-regulated on T-cells after activation, and effectively serves as a “brake” on T-cell activation.
- Ipilimumab is a human monoclonal antibody against CTLA-4 that inhibits this brake, and enhances T-cell activation.
  - It has been demonstrated to have beneficial activity in advanced melanoma in Phase 2 trials (O'Day, Ann Oncol, 2010).
- This Phase III study compared the efficacy and safety of ipilimumab monotherapy vs. gp100 monotherapy vs. combination therapy.

Methods

- Eligibility:
  - HLA-A*0201 positive, previously treated adults with unresectable stage III/IV melanoma.
- Patients accrued in 125 centers worldwide, stratified by M-stage and prior IL-2 therapy, and then randomized in a 1:3:1 ratio to:
  - Ipilimumab (3 mg/kg q3w x 4 doses) + placebo (n=137),
  - Ipilimumab + gp100 (n=403), or
  - gp100 + placebo (n=136).
- Primary endpoint: overall survival (OS) between patients who received combination versus gp100 alone (control arm).
  - The study was initially powered for best overall response rate (BORR), but this was changed to OS before unblinding.
- Secondary endpoints: all other OS comparisons, BORR, disease control rate (DCR), progression-free survival (PFS), and safety.

**Results**

- Patients enrolled on the different treatment arms were well-balanced.
- Enrolled patients were poor risk: 70% had Stage M1c (visceral non-lung metastases), and 40% had an elevation in their serum LDH.
- Overall survival:
  - The study demonstrated a statistically significant improvement in OS for patients receiving Ipilimumab (with or without gp100) versus gp100 alone: (see table below)
  - At 1 year: 46% with Ipilimumab alone vs. 25% with gp100 alone.
  - At 2 years: 24% with Ipilimumab alone vs. 14% with gp100 alone.
  - Median OS: 6.4 months with gp100 alone vs. 10.1 months with Ipilimumab
  - HR=0.66 for Ipilimumab vs. gp100 alone (p=0.0026)

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab</th>
<th>Ipilimumab+gp100</th>
<th>gp100</th>
<th>Ipilimumab vs. gp100</th>
<th>Ipilimumab+gp100 vs. gp100</th>
<th>Ipilimumab+gp100 vs. ipilimumab</th>
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<tbody>
<tr>
<td><strong>OS rate, %</strong></td>
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<td></td>
<td></td>
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<tr>
<td>12 mos.</td>
<td>46</td>
<td>44</td>
<td>25</td>
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<td>24 mos.</td>
<td>24</td>
<td>22</td>
<td>14</td>
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<tr>
<td><strong>OS, median, mos.</strong></td>
<td>10.1</td>
<td>10</td>
<td>6.4</td>
<td>HR=0.66</td>
<td>HR=0.68</td>
<td>HR=1.04</td>
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<td></td>
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<td></td>
<td>p=0.0026</td>
<td>p=0.0004</td>
<td>p=0.7575</td>
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<tr>
<td><strong>PFS, median, mos.</strong></td>
<td>2.9</td>
<td>2.8</td>
<td>2.8</td>
<td>HR=0.64</td>
<td>HR=0.81</td>
<td>HR=1.25</td>
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<td>p=0.0007</td>
<td>p=0.0464</td>
<td>p=0.0371</td>
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<tr>
<td><strong>DCR, %</strong></td>
<td>28.5</td>
<td>20.1</td>
<td>11</td>
<td>p=0.0002</td>
<td>p=0.0179</td>
<td>p=0.0429</td>
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<tr>
<td><strong>BORR%</strong></td>
<td>10.9</td>
<td>5.7</td>
<td>1.5</td>
<td>p=0.0012</td>
<td>p=0.0433</td>
<td>p=0.0402</td>
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*Medians are similar; however, PFS curves part after the median as reflected by HR.

- Significant differences in DCR, BORR, and PFS were observed.
- For these outcomes, patients treated with ipilimumab alone did better than those treated with the combination, although both groups fared better than gp100 alone.
- Severe adverse events tended to be immune-related GI toxicity (colitis and perforation) and occurred in 23% of Ipilimumab alone patients and 17% of patients treated with the combination.

**Authors’ Conclusions**

- Ipilimumab is the first agent to improve overall survival in a phase III study of previously treated patients with advanced...
The addition of gp100 vaccine to ipilimumab did not improve outcomes relative to ipilimumab alone, and actually led to inferior rates of secondary endpoint measures of disease control, best objective response, and progression-free survival. However, it did not affect overall survival rates or the safety profile.

Ipilimumab is a promising agent for immune modulation that should be explored in NSCLC and metastatic prostate cancer.

**Clinical Implications**

- This exciting study is the first Phase III trial to demonstrate an overall survival benefit in previously treated patients with advanced melanoma - a particularly challenging group of patients.
  - The arm receiving gp100 vaccine alone appears to be an appropriate control group, when OS rates for this group are compared to those reported in a prior meta-analysis (Korn, JCO, 2008)
  - Therefore, the impressive OS advantage reported here can be assumed to be relative to standard first-line therapy.
- In this study, ipilimumab alone appeared to be superior to the combination of ipilimumab and gp100 vaccine, which is intriguing because ipilimumab (unlike gp100 vaccine) is not specific to melanoma, but rather acts upon the immunomodulatory molecule CTLA-4;
  - This suggests that ipilimumab may in fact have activity in a number of different types of cancer that are effective at evading immune surveillance.
  - Therefore, it would be justified to explore the clinical utility of this antibody in other sites of metastatic disease that are refractory to current therapies.

- Unanswered questions:
  - This study included only HLA-A*0201 positive patients (because gp100 peptide is HLA-A2 restricted); in the future, if gp100 is excluded from this treatment regimen, which patients would be considered eligible for treatment?
  - The dose of ipilimumab used in this study (3 mg/kg) was outperformed in a previous dose finding study by the 10 mg/kg dose, so it is unclear if this study used the optimal dose and scheduling of the drug.
  - The control used in this study (gp100 vaccine) is questionable, because there is no standard of care for salvage after first line treatment in advanced melanoma.
  - Ipilimumab is a potent activator of the immune system, and safe treatment requires aggressive surveillance in order to recognize serious adverse events; this may not be feasible in a community setting.
  - The question of whether ipilimumab may have a role as part of adjuvant treatment for resected melanoma remains outstanding.
- In sum, ipilimumab is the first agent to improve overall survival of patients with advanced melanoma in a Phase III trial, and has an intriguing mechanism of action that may be applicable across different disease sites. Nevertheless, at this time the treatment of choice for patients with advanced melanoma remains a clinical trial, as several questions remain unanswered about how best to integrate this agent into clinic practice.