A Case Study: Ipilimumab in Pre-treated Metastatic Melanoma

Tai-Tsang Chen, PhD
Global Biometric Sciences, Bristol-Myers Squibb
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Disclosure

• Employment: currently employed by Bristol-Myers Squibb as Head of Global Biometric Sciences in Medical and Market Access

• The views expressed in this presentation are personal based on my experience and do not necessarily reflect the views of Bristol-Myers Squibb
## Advanced Melanoma: Approved Agents Prior to 2011

<table>
<thead>
<tr>
<th></th>
<th>DTIC N=117</th>
<th>IL-2 N=270</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age (yrs)</strong></td>
<td>55</td>
<td>42</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>5.6</td>
<td>11.4</td>
</tr>
<tr>
<td>1 year survival (%)</td>
<td>24</td>
<td>43</td>
</tr>
<tr>
<td>2 year survival (%)</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td><strong>Safety (Grade 3-4 Toxicity)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension (%)</td>
<td>—</td>
<td>45</td>
</tr>
<tr>
<td>Renal insufficiency (%)</td>
<td>—</td>
<td>39</td>
</tr>
<tr>
<td>Thrombocytopenia (%)</td>
<td>6</td>
<td>17</td>
</tr>
</tbody>
</table>


Bristol-Myers Squibb
No Significant Improvement in OS on DTIC Over Time

Median survival: ~ 6 - 8 months
1 year survival: ~ 24% – 30%
2 year survival: ~ 10%

Source

- Chapman, 1999 121
- Middleton, 2000 149
- Avril, 2004 117
- Bedikian, 2006 385
Immunotherapy Approved in the US

• 1992
  – IL-2 for the treatment of renal cell cancer
• 1996
  – Interferon for the treatment of adjuvant melanoma
• 1998
  – BCG for the treatment of bladder cancer
  – IL-2 for the treatment of advanced melanoma
• 2009
  – Sipuleucel-T for the treatment of prostate cancer
Ipilimumab: Blocks CTLA-4, Potentiates T-Cell Function

- **T-cell activation**
  - APC
  - CD28
  - TCR
  - HLA
  - B7

- **T-cell inactivation**
  - APC
  - CTLA-4

- **T-cell activation**
  - APC
  - Ipilimumab
Ipilimumab Development Milestones

**Preclinical science**
- B7-1 and B7-2 are CTLA4 ligands
- Cloning of CTLA4 gene

**Clinical science**
- Treatment of mouse tumours with CTLA4
- First patient treated
- CVCTWG workshop suggesting new response kinetics and criteria

**Phase II:**
- Novel responses
- Delayed separation of KM curves for OS

**Phase III:**
- Primary endpoints of two Phase III trials changed to OS
- No OS interim analyses
- CIC and BMS: immune-related response criteria

- Phase III positive on OS
- Regulatory approval in the USA

- Regulatory science milestones
- Conventional clinical milestones
- Novel clinical science milestones
- CIC workshops driving changes in clinical science
Ipilimumab Development Milestones (cont’d)

- MDX010-20 was the first trial that shows OS benefit in 30 years
- Previously treated and untreated metastatic melanoma
  - US approval: March, 2011
- Previously treated metastatic melanoma
  - EU approval: July, 2011
  - NICE appraisal: December, 2012
- Previously untreated metastatic melanoma
  - EU approval: November, 2013
  - NICE appraisal: July, 2014
Key Clinical Evidence
MDX010-20: Phase 3 Study Design

<table>
<thead>
<tr>
<th>Screening</th>
<th>Induction</th>
<th>≥ 1 Re-induction in eligible patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-A*0201 Pre-treated advanced melanoma N=676</td>
<td>Ipilimumab (3mg/kg) + gp100 n=403</td>
<td>Ipilimumab (3mg/kg) + gp100</td>
</tr>
<tr>
<td></td>
<td>Ipilimumab (3 mg/kg) + placebo n=137</td>
<td>Ipilimumab (3 mg/kg) + placebo</td>
</tr>
<tr>
<td></td>
<td>gp100 + placebo n=136</td>
<td>gp100 + placebo</td>
</tr>
</tbody>
</table>
Key Clinical Evidence
MDX010-20 Study Design History

Original Study Design
• Contribution of components
  – Early phase II data
    • Durable responses
    • No OS data
  – Primary endpoint: BORR

Revised Study Design (before unblinding)
• Survival superiority
  – Additional phase II data
    • BORR inadequate
    • Long-term survival
  – Primary endpoint: OS
MDX010-20 Ipilimumab in Previously Treated Stage III/IV Melanoma (Overall Survival)

- Ipi/gp100 vs. gp100
  - HR: 0.68 (0.55, 0.85)
  - P<0.001

- Ipi vs. gp100
  - HR: 0.66 (0.51, 0.87)
  - P<0.003

- No added benefit of gp100

Hodi FS et al. (2010) NEJM.

Cancer Immunology Research: Cancer Immunology at the Crossroads
Challenges

• No direct comparison between ipilimumab and frequently used chemotherapies
• The standard of care for metastatic melanoma has been referral to clinical trials due to lack of efficacy
• Key clinical evidence compared ipilimumab 3 mg/kg to gp100
• In the absence of head to head comparison between ipilimumab 3 mg/kg against other therapies,
  – NMA was conducted to inform treatment selection
  – Additional analysis conducted to show similarity between gp100 and chemotherapy treatment effect
NMA: Study Selection

- A systematic literature review to synthesize available OS evidence of systemic therapies

**Box 1. Scope of systematic literature review**

**Population:** pretreated adult patients with unresectable (stage III/IV) melanoma, with or without BM. Studies which included a proportion of pretreated patients and systemic treatment-naive patients (ie, mixed line population) were also included in order to maximize the evidence base.

**Interventions:** ipilimumab, interferon-alpha (IFN-α)/IFN-γ, interleukin-2 (IL-2), dacarbazine (DTIC), temozolomide, cisplatin, carboplatin, paclitaxel, fotemustine, melanoma vaccines, and placebo.

**Comparators:** studies that compare the agents (listed under “Interventions”) to each other as monotherapies, combination therapies with one another, combination therapies with another agent not listed under “Interventions” (ie, not of interest), or best supportive care.

**Outcomes:** survival endpoints reported at interim time points such as median OS, percentage of patients alive, or hazard ratios.

**Study designs:** RCTs, including open-label extensions and crossover studies; phase 2 and above. Full-text publications from peer-reviewed journals, clinical study reports (CSRs), or conference abstracts should be available, and in English.

15 studies to form one interlinked network

25 studies showed OS KM curves
Second Ipilimumab study included in the NMA: Ipilimumab in Patients with Previously Treated Advanced Melanoma

NMA Methodology

- Parametric network meta-analysis* (NMA) of treatment effect
  - Shape parameter
  - Scale parameter

- Parametric modeling potentially addresses non-proportionality

- Estimation of parameters was carried out using a fixed-effects and random-effects Weibull and Gompertz models

- Models were compared using Deviance Information Criterion (DIC)

- Fixed-effects Gompertz model was selected
Hazard Ratio Over Time:
Fixed-Effects Gompertz NMA Model
Overall Survival: Fixed-Effects Gompertz NMA Model
Probability of Greatest Survival Benefit Over time: Fixed-Effects Gompertz NMA Model
Findings from NMA

• 3 mg/kg ipilimumab is expected to have greater OS compared to other existing therapies for the management of pretreated patients with unresectable stage III or IV melanoma

• Limitations
  – Compatibility of studies included in NMA
  – Inclusion and exclusion of studies in NMA
  – Grouping of studies by class in NMA
Key Question: GP100 Treatment Effect (OS)

• An analysis was performed by BMS
  – To understand the effect of gp100 on OS
  – To evaluate results in this arm relative to historical data for patients with advanced melanoma

• The objective of this analysis was to show that the observed OS in gp100 arm was representative of that from chemotherapies in the absence of a randomized comparison

• A prognostic model for advanced melanoma (Korn et al.) was adopted to estimate the OS had the same group of patients been treated with chemotherapies
Meta-Analysis Methodology (Korn et al.)

• Objective:
  - Develop benchmarks for OS and PFS for future studies

• Materials and Method:
  - 1278 patients in 42 cooperative group trials across different regiments from 1975 to 2005 were included
  - Multivariate analyses were performed to fit the key prognostic factors

• A multivariate analysis presented in the paper identified the following factors as predictors (key prognostic factors) for OS:
  - Individual patient baseline characteristics: performance status, presence of visceral metastases, and gender
  - Trial-level characteristics: the inclusion of central nervous system (CNS) metastases or not

• Reference curve was produced to allow prediction of OS based on the distributions of key prognostic factors
BMS applied the Korn model to generate the predicted OS curve for the gp100 arm of

- The resulting predicted survival curve was consistent with the observed OS data in the gp100 arm.
- Survival results from this arm were not different from what would be expected in this population (one sample log-rank p = 0.25)
One-Year Milestone Survival

- The 95% confidence bounds suggest that no trial arm has a statistically different rate from the overall mean 1-year rate of 25% (524 of 2,075 patients).
- The 1-year milestone survival rate from MDX010-20
  - Ipilimumab+gp100: 0.436
  - Ipilimumab: 0.456
  - Gp100: 0.253
Estimated Overall Survival Adjusted for Prognostic Factors

- gp100
- Ipilimumab 3 mg/kg
- Ipilimumab 3 mg/kg + gp100
- Ipilimumab 0.3 mg/kg
- Ipilimumab 10 mg/kg
- Paclitaxel 100 mg/m²
- Paclitaxel 80 mg/m² + carboplatin 200 mg/m²
- Placebo
- Paclitaxel 225 mg/m² + carboplatin AUC 6 + placebo
- Paclitaxel + carboplatin + sorafenib

Proportion of patients alive (%) vs. Months
## Estimated Expected Efficacy from 25 Studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Expected survival, months (95% Cr)</th>
<th>Median survival, months (95% Cr)</th>
<th>% patients alive at 12 months</th>
<th>% patients alive at 24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab 10 mg/kg</td>
<td>18.1 (12.5, 26.7)</td>
<td>10 (7.15)</td>
<td>46.5</td>
<td>26.4</td>
</tr>
<tr>
<td>Ipilimumab 3 mg/kg</td>
<td>16.7 (12.8, 22.4)</td>
<td>10 (8.13)</td>
<td>45.6</td>
<td>24.3</td>
</tr>
<tr>
<td>Ipilimumab 3 mg/kg + gp100</td>
<td>16.2 (11.4, 23.1)</td>
<td>10 (7.14)</td>
<td>45.6</td>
<td>23.5</td>
</tr>
<tr>
<td>Ipilimumab 0.3 mg/kg</td>
<td>13.2 (6.6, 26.8)</td>
<td>8 (6.11)</td>
<td>37.8</td>
<td>17.6</td>
</tr>
<tr>
<td>Paclitaxel 225 mg/m² + carboplatin AUC 6 + placebo</td>
<td>11.6 (6.6, 14.9)</td>
<td>9 (6.11)</td>
<td>40.3</td>
<td>12.1</td>
</tr>
<tr>
<td>Placebo</td>
<td>10.5 (6.6, 13.9)</td>
<td>7 (6.09)</td>
<td>34.0</td>
<td>11.3</td>
</tr>
<tr>
<td>Paclitaxel 225 mg/m² + carboplatin AUC 6 + sorafenib 400 mg</td>
<td>10.4 (6.8, 13.2)</td>
<td>8 (7.10)</td>
<td>36.1</td>
<td>8.7</td>
</tr>
<tr>
<td>gp100 + placebo</td>
<td>10.1 (6.9, 14.9)</td>
<td>7 (5.10)</td>
<td>32.1</td>
<td>10.6</td>
</tr>
<tr>
<td>Paclitaxel 80 mg/m² + carboplatin 200 mg/m²</td>
<td>2.9 (1.1, 12.6)</td>
<td>1 (0.3)</td>
<td>6.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Paclitaxel 100 mg/m²</td>
<td>2.1 (0.9, 24.3)</td>
<td>1 (0.2)</td>
<td>7.1</td>
<td>4.7</td>
</tr>
<tr>
<td>Mixed (treatment-naive and pretreated) population</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ipilimumab combinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipilimumab 3 mg/kg + DTIC 250 mg/m²</td>
<td>21.5 (12.9, 34.7)</td>
<td>14 (6.24)</td>
<td>56.1</td>
<td>22.9</td>
</tr>
<tr>
<td>Ipilimumab 10 mg/kg + budesonide 9 mg</td>
<td>14.2 (11.1, 18.9)</td>
<td>11 (6.47)</td>
<td>47.4</td>
<td>19.2</td>
</tr>
<tr>
<td>Chemotherapy alone</td>
<td>DTIC 1200 mg/m²</td>
<td>12 (5.3, 37.5)</td>
<td>5 (0.13)</td>
<td>30.8</td>
</tr>
<tr>
<td>DTIC 250 mg/m²</td>
<td>8.5 (5.2, 19.9)</td>
<td>5 (0.19)</td>
<td>25.7</td>
<td>9.3</td>
</tr>
<tr>
<td>Chemotherapy combinations</td>
<td>DTIC 220 mg/m² + cisplatin 35 mg/m² + carbamustine 150 mg/m² + tamoxifen 20 mg/m²</td>
<td>17.7 (13.1, 28.4)</td>
<td>12 (6.18)</td>
<td>50.1</td>
</tr>
<tr>
<td>DTIC 220 mg/m² + cisplatin 25 mg/m² + carbamustine 100 mg/m² + tamoxifen 40 mg</td>
<td>5.7 (4.2, 8.9)</td>
<td>4 (0.2)</td>
<td>13.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Bio-chemotherapy combinations</td>
<td>DTIC 220 mg/m² + cisplatin 35 mg/m² + carbamustine 150 mg/m² + tamoxifen 20 mg/m² + IL-2 + IFN-α</td>
<td>16.3 (12.9, 21.8)</td>
<td>12 (6.16)</td>
<td>52.6</td>
</tr>
<tr>
<td>Bio-chemotherapy combinations</td>
<td>DTIC 220 mg/m² + cisplatin 25 mg/m² + carbamustine 100 mg/m² + tamoxifen 40 mg + IL-2 + IFN-α</td>
<td>4.7 (3.6, 6)</td>
<td>4 (0.3)</td>
<td>4.0</td>
</tr>
<tr>
<td>Immunotherapy alone</td>
<td>IL-2 720,000 MIU/m²</td>
<td>11.9 (7.3, 18.9)</td>
<td>9 (5.13)</td>
<td>38.8</td>
</tr>
<tr>
<td>IL-2 3 or 2 MIU/m²</td>
<td>8.6 (7.3, 10.3)</td>
<td>6 (0.5)</td>
<td>27.2</td>
<td>8.3</td>
</tr>
<tr>
<td>Immunotherapy combinations</td>
<td>IL-2 4.5 MIU/m² + IFN-23 3 MIU/m²</td>
<td>9.7 (7.1, 14.4)</td>
<td>6 (4.0)</td>
<td>30.8</td>
</tr>
<tr>
<td>Immunotherapy combinations</td>
<td>IL-2 18 MIU/m² + IFN-α 10 MIU/m²</td>
<td>9.2 (7.1, 11.2)</td>
<td>6 (4.0)</td>
<td>30.8</td>
</tr>
</tbody>
</table>
Conclusion

Network Meta-Analysis

• NMA was not included in NICE STA for Ipilimumab in previously treated melanoma patients
• Subsequent NMA was conducted by grouping 15 studies in 8 treatment classes
• Limitations of NMA include grouping of treatments and selection of studies

Benchmark Meta-Analysis Modeling (Korn et al.)

• Predicted OS adjusting for key prognostic factors showed OS benefit compared to chemotherapies
• Some key prognostic factors such as LDH not captured
Reference (in chronological order)