Facilitating the Development of Immunotherapies: Intermediate Endpoints for Immune Checkpoint Modulators
Immune Checkpoint Modulators

Jim Allison, Ph.D.
The University of Texas
MD Anderson Cancer Center
Why immunotherapy?

Specificity

Memory

Adaptability
CTLA-4 Blockade Enhances Tumor-Specific Immune Responses

Attenuated or Terminated Proliferation

Unrestrained Proliferation

IL-2
Evolution of Response: Patient Example

**Screening**

**Week 12**
Initial increase in total tumor burden (mWHO PD)

**Week 16**
Responding

**Week 72**
Durable & ongoing response without signs of IRAEs

20006

Courtesy of K. Harmankaya
Kaplan-Meier Analysis of Survival

<table>
<thead>
<tr>
<th>Survival Rate</th>
<th>Ipi + gp100 N=403</th>
<th>Ipi + pbo N=137</th>
<th>gp100 + pbo N=136</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>44%</td>
<td>46%</td>
<td>25%</td>
</tr>
<tr>
<td>2 year</td>
<td>22%</td>
<td>24%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Hodi et al. NEJM 2010
Programmed Death 1

http://www.melanoma.org/community/mpip-melanoma-patients-information-page/video-how-anti-pd-1-therapy-works-immune-system
Anti – PD-1 (BMS-936558)

296 Patients with Metastatic Cancer
1, 3, 10 mg/kg, MTD not reached

Safety: Adverse events similar to Ipilimumab, but 4% pneumonitis (3 deaths)

Clinical Activity:
- Melamona (n= 94): 28% CR/PR, 6% SD
- NSCLC (n=76): 18% CR/PR, 7% SD
- RCC (n= 33): 27% CR/PR, 27% SD
- CRC (n=19), CRPC (n=13): No responses

Topalian ASCO, NEJM 2012
Clinical Activity in Melanoma Patients Receiving Ipilimumab (αCTLA-4) and Nivolumab (αPD-1)

ASCO 2013
NEJM 6/2/2013
Improving Survival with Combination Therapy
Improving Survival with Combination Therapy

Control
Conventional Therapy
Immunotherapy (e.g. anti-CTLA4)
Improving Survival with Combination Therapy

- Control
- Conventional Therapy
- Immunotherapy (e.g. anti-CTLA4)
- Combination

The graph shows the survival time for different treatment options. The combination therapy (green) extends the survival time significantly compared to the control and conventional therapy.
Speakers

• Jim Allison, Ph.D., U.Texas MD Anderson Cancer Center
• Mark Gorman, Survivor and Advocate
• Ramy Ibrahim, M.D. MedImmune
• Axel Hoos, M.D., Ph.D, Glaxo-Smith Kline
• Tai-Tsang Chen, Ph.D., Bristol-Myers Squibb
• Steve Rosenberg, M.D., Ph.D., National Cancer Institute
• Amy McKee, M.D., FDA-CDER
• Celia Witten, M.D., Ph.D., FDA-CBER

Contributors: Renzo Canetta, M.D., Suzanne Topalian, M.D.
Mark Gorman
Long-term Survivor of Metastatic Melanoma
And Patient Advocate
Immunotherapies: Dosing Challenges

Ramy Ibrahim, M.D.
MedImmune
Conventional dose/schedule selection and anti-cancer development

• Preclinical data from efficacy studies to identify target exposures in human
• Escalate doses in FTIH studies to assess safety and achieve target exposures (or higher) to increase likelihood of early signal
• Determine the MTD after DLTs are observed
• Select MTD for further development in randomized studies to assess efficacy
• Initiate registrational studies
Novelties with immune-modulators and implications on dose/schedule selection

- Animal data might not inform dose selection
  - Cross reactivity and finding surrogate has limitations

- The “target” is the immune system and not the cancer
  - Complexity of the interaction between the immune system and cancer
  - Patients might have different threshold or sensitivity to immune priming
    - We need to identify a dose that achieves appropriate exposure while accommodating inter-patient variability

- Immune targets are dynamic
  - Variability in target level, site of expression, tumor type and tumor burden

- Animal data and PK modeling might only inform the starting dose and identify a target exposure range
Novelties with immune-modulators and implications on dose/schedule selection (cont)

• Dose escalation till “toxicity” is not a viable approach
  • None of the PD1/PDL1 targeting antibodies reached an MTD
  • Activity observed at multiple dose levels
  • Early phase clinical PK, target related biomarkers, markers of immune response and clinical activity should be leveraged
  • Need for novel phase I designs to inform dose selection
Novelties with immune-modulators and implications on dose/schedule selection (cont)

◆ Dose-ranging comparative studies may not necessarily better inform dose selection
  – Tremelimumab development
    • Randomized phase II suggested 15 mg/kg q3mo to be associated with more favorable risk: benefit
    • Phase III study suggested 15mg/kg Q 3 months not to maintain desired AUC
    • Currently exploring monthly dosing

◆ Beside dose/schedule, what about duration of treatment?

◆ Due to the early and sometimes dramatic signal of activity, programs progress quickly from large phase 1 to phase 3
  – How to design better studies to inform registrational studies
Delayed Treatment Effects of Cancer Immunotherapies

Axel Hoos, M.D., Ph.D.
Glaxo-Smith Kline
A Methodological Framework for Immuno-Oncology

**Challenge:** Clinical trial endpoints are not immunotherapy-focused

**Solution:** Adjustment of endpoints to immunotherapy biology

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Review

Lessons from randomized phase III studies with active cancer immunotherapies—Outcomes from the 2006 Meeting of the Cancer Vaccine Consortium (CVC)

Lothar H. Finke a,g,*, Kerry Wentworth b,g, Brent Blumentstein c, Natalie S. Rudolph d, Hyam Levitsky e,g, Axel Hoos e,g

Vaccine 2007

Improved Endpoints for Cancer Immunotherapy Trials


J Natl Cancer Inst 2010

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Survival: Conventional Design Assumptions

- No events occur before separation of curve
- Proportional hazard applies
Delayed Separation – Sipuleucel-T

Separation of curves at ~8 months

Sponsor: Dendreon
Agent: autologous dendritic cell vaccine
Disease: hormone-refractory prostate cancer

Kantoff et al., New Engl. J. Med. 2010
Delayed Separation – Ipilimumab

Separation of curves at ~4 months

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**A. Overall Survival**

- **Ipi + gp100 vs. gp100:** HR 0.68 (0.55-0.85), p=0.0004
- **Ipi vs. gp100:** HR 0.66 (0.51-0.87), p=0.0026
- **Ipi + gp100 vs. ipi:** HR 1.04 (0.83-1.30), p=0.7575

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**Sponsor:** BMS

**Agent:** Anti-CTLA-4 mAb

**Disease:** Metastatic melanoma

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Hodi et al., New Engl. J. Med. 2010
Implications of Delayed Separation of Curves

- Model Scenario -

**HR\textsuperscript{overall} = Hazard ratio for entire curve**

**HR\textsubscript{E} = Early Hazard Ratio (before Separation)**

**HR\textsubscript{L} = Delayed Hazard Ratio (after separation)**

*Large \( \Delta \) after separation needed to compensate for no effect before separation*
Interactions between Immune System and Tumor

Tumor Volume Increase Due to Lymphocyte Infiltration

Ribas et al., Clin Cancer Res 2009; 15:7116–8
Immunotherapy Patterns of Response

Conventional Response

Prolonged Stable Disease

Delayed Response

Response with New Lesions

Anti-CTLA-4 (Ipilimumab): Delayed Response

O’Regan, KN, et al. AJR 2011
Regression of metastatic RCC following anti-PD-1 therapy, with “immune-related” response characteristics.

Autologous DC + IFN α2b in Advanced Melanoma: Delayed Response

Wilgenhof S. et al., Melanoma Res. 2011
Tumor Growth Rate: Potential Impact on Survival

Available Tools

• Statistical methods for analyzing survival
• Immune-related Response Criteria
• Tumor growth kinetics
Intermediate Endpoints for Immune Checkpoint Modulators: Milestone OS Analysis

Tai-Tsang Chen, Ph.D.
Bristol-Myers Squibb
Rationale

• Unique characteristics of immune checkpoint modulators
  – Survival probability (long term survival)
  – Delayed clinical effect

• Key challenges of log-rank analysis as sole characterization of overall survival
  – Does not capture key attribute of survival probability (or long term survival)
  – Time to final analysis may continue to lengthen based on kinetics of survival effect
Milestone OS Analysis

• Milestone survival is defined as the Kaplan-Meier survival probability at a pre-specified milestone, e.g., 2 years

• Study design and analysis consideration
  – Primary endpoint: overall survival
  – Intermediate endpoint: milestone survival probability
  – Population includes patients with a minimal follow-up duration, i.e., ≥ milestone duration
  – Hierarchical testing procedure
Example*: Ipilimumab+DTIC vs. DTIC Final OS Analysis

CA184-024 OS (N=502)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>OS HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>0.716</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Example*: Ipilimumab+DTIC vs. DTIC Intermediate 2-year Milestone OS Analysis

CA184-024  
**KM-2 yr OS (N=300)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>24 month OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (C vs. E)</td>
<td>14.1% vs. 24.9%</td>
</tr>
<tr>
<td>P-value</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Pros and Cons

• Pros
  – Potential earlier assessment of benefit/risk
  – Greater statistical power when delayed treatment effect is present
  – Direct characterization of survival probability (long term survival effect)
  – Predictable timing of analysis
  – Both intermediate and final endpoints are overall survival

• Cons
  – Challenge in maintaining study integrity post milestone analysis, i.e., unblinding prior to final OS analysis
  – Does not account for the totality of OS data
  – Only appropriate for a registration trial when prior data enable an understanding of appropriate milestone time point selection
Steven Rosenberg, M.D., Ph.D.

National Cancer Institute
2013 Conference on Clinical Cancer Research

Amy McKee, M.D.

FDA
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