Game Plan for Therapeutic Cancer Vaccines

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Clinipace Worldwide: Oncology Drug Development

★ Drug Development
★ Regulatory
★ Clinical Development
★ Pharmacovigilance
★ Post-Approval

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VOI Publications
★ The Oncology Roadmap
★ pharmahandbook®
<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Whole Cell Vaccines</th>
<th>Antigen/Adjuvant Vaccines</th>
<th>Viral Vector / DNA-based Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Autologous</td>
<td>GM2 ganglioside vaccine combined with the QS-21 adjuvant (GMK)</td>
<td>plasmid DNA vaccine expressing the Melan-A/MART antigen</td>
</tr>
<tr>
<td>Dendritic Cell Vaccines</td>
<td>Allogeneic</td>
<td>Effective, but inferior to high-dose IFN (another immunotherapy) in Phase III trial</td>
<td>Melan-A/MART-1 specific T cell responses were evident by ELISpot, but no HBsAg-specific antibodies detected</td>
</tr>
<tr>
<td>Provenge (sipuleucel-T), is the first approved cell-based vaccine</td>
<td>CanVaxin™, irradiated allogeneic melanoma cell line plus BCG</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Trends in Cancer Vaccine Development & Lessons Learned
~230 vaccines are in clinical development

Melanoma, breast, and lung have the highest overall activity

Lung cancer has more late-stage candidates

- 81 Phase I
- 75 Phase I/II
- 65 Phase II
- 2 Phase II/III
- 8 Phase III

Source: Dayoub, E., Davis, MM. Relationship of therapeutic cancer vaccine development to population disease burden and five-year survival. Human Vaccines Nov 2011; Data H1 2011
Geography of Cancer Vaccine Research

Site Locations for Phase III Cancer Trials

- **Non-Vaccine Phase III Pivotal Trials (2005-2011)**
- **Vaccine Phase III Trials**

### Sources:
Pivotal trial data from *Oncology Clinical Trials: The Roadmap to FDA Approval*, VOI Consulting / insiteinvestigator database; Vaccine trial locations from clinicaltrials.gov and published articles on Phase III trials
**Trial Design**

**PRIMARY ENDPOINT**
Vaccine trials are much more likely than other cancer studies to feature overall survival as a primary endpoint:

- Non-vaccine Phase III Pivotal Trials (2005-2011)
- Vaccine

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine</th>
<th>Non-vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression Free Survival</td>
<td>37%</td>
<td>0%</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>69%</td>
<td>22%</td>
</tr>
<tr>
<td>Time to Progression</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>Disease Free Survival</td>
<td>6%</td>
<td>15%</td>
</tr>
<tr>
<td>Response Rate</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Other</td>
<td>12%</td>
<td>12%</td>
</tr>
</tbody>
</table>

**COMPARISON ARM**
Placebo controls are also much more common:

- Active: 62%
- Passive: 20%
- Placebo: 24%

**RANDOMIZATION**
Vaccine trials also tend to overweight the investigative arm: ~75% of Phase III studies have 2:1 randomization as compared to >10% of non-vaccine pivotal cancer trials.

Sources: Pivotal trial data from *Oncology Clinical Trials: The Roadmap to FDA Approval*. VOI Consulting / insiteinvestigator database; Vaccine trial data from clinicaltrials.gov and published sources. Passive controls can take the form of comparisons to best supportive care or the lack of investigational drug in the comparison arm.
### Trial Size

Cancer vaccine trials, on average, are smaller than Phase III pivotal trials for other cancer drugs. However, cancer vaccine trials currently underway are very similar in terms of # of patient & sites.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Phase III Trial Type</th>
<th>Average</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
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</thead>
<tbody>
<tr>
<td>Number Patients</td>
<td>Non-Vaccine (Actual)</td>
<td>667</td>
<td>571</td>
<td>100</td>
<td>3387</td>
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<tr>
<td></td>
<td>Vaccine (Actual)</td>
<td>256</td>
<td>177</td>
<td>98</td>
<td>512</td>
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<tr>
<td></td>
<td>Vaccines (Projected)</td>
<td>687</td>
<td>568</td>
<td>230</td>
<td>1476</td>
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<tr>
<td>Number of Sites</td>
<td>Non-Vaccine (Actual)</td>
<td>106</td>
<td>88</td>
<td>19</td>
<td>476</td>
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<tr>
<td></td>
<td>Vaccine (Actual)</td>
<td>40</td>
<td>27</td>
<td>17</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Vaccines (Projected)</td>
<td>108</td>
<td>76</td>
<td>10</td>
<td>295</td>
</tr>
</tbody>
</table>

Sources: Actual trial data from *Oncology Clinical Trials: The Roadmap to FDA Approval*. VOI Consulting / insiteinvestigator database; Projected vaccine trials data from clinicaltrials.gov.
To date, Phase III cancer vaccine trials have experienced substantially lower randomization rates. This problem has led to a discontinuation of at least one trial (i.e. BiovaxID had a 563 patient target but enrolled only 234 after ~8 years).

Slow accrual may be due in part to high screen failure rates for vaccine trials (average = 29% as compared to <20% for pivotal trials of other cancer drugs).

Provenge (D9901)

- Screened = 186
- Randomized = 127 (68%)
- Excluded = 59 (32%)

Provenge (D9902A)

- Screened = 116
- Randomized = 98 (84%)
- Excluded = 18 (16%)

Provenge (D9902B)

- Screened = 926
- Randomized = 512 (55%)
- Excluded = 414 (45%)

BiovaxID

- Screened = 234
- Randomized = 177 (76%)
- Excluded = 57 (24%)

mitumprotimut-T

- Screened = 495
- Randomized = 364 (74%)
- Excluded = 131 (26%)

Source: Oncology Clinical Trials: The Roadmap to FDA Approval. VOI Consulting / insiteinvestigator database
In comparison to the design and execution of other types of cancer trials, vaccine studies show more similarities than differences (e.g. number patients, number sites, locations).

Nonetheless, there are important differences:

- Overall survival strongly preferred as primary endpoint.
- Placebo controls and 2:1 randomization are the norm.
- Expect high screen failure and slower randomization rates.
- Fewer sites with vaccine experience particularly in developing markets (with the exception of Central/Eastern Europe).
- Expect strict regulatory scrutiny regarding efficacy and labeling that reflects the studied population.
Regulatory Strategy
Regulated by FDA’s Center for Biologics Evaluation and Research

Reviewed by Office of Cellular, Tissue and Gene Therapy (CBER)
  - CDER and CDRH may be involved in product review

Investigational New Drug (IND) application required for clinical trials in humans. FDA strongly recommends a pre-IND meeting to discuss study design, CMC and nonclinical (toxicology) plans

Biologics License Application (BLA) required for marketing approval

In parallel, device approval may be required for delivery device, companion diagnostic
Regulatory Challenges

- CMC can be very difficult
- Patient selection
- Conventional dose-escalation to reach MTD not relevant
- Use of adjuvants, companion diagnostic, delivery device
- Clinical response is often delayed
- Need to develop standardized assays
- Importance of placebo vs. active comparator group
- Standard clinically meaningful endpoint may not be relevant
Overview of ATMPs

- European Legislation differentiates between Small Molecule Entities (SMPs) and Advanced Therapy Medicinal Products (ATMPs)
- Different Competent Authority (CA) and Ethics Committee (EC) approval timelines
- Separate GCP Guidelines for ATMPs
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<th>Month 2</th>
<th>Month 3</th>
<th>Month 4</th>
<th>Month 5</th>
<th>Month 6</th>
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<td>1</td>
<td>Total elapsed time</td>
<td>24W</td>
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<td>2</td>
<td>Compilation of submission</td>
<td>5W</td>
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<td>3</td>
<td>Competent Authority</td>
<td>5W</td>
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<td>4 to 6 weeks</td>
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<tr>
<td>4</td>
<td>Ethics Committee</td>
<td>10W</td>
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<td>5</td>
<td>Site-specific assessment</td>
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<td>6 to 12 weeks</td>
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<td>R&amp;D (UK only)</td>
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<td></td>
<td>6 to 12 weeks</td>
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<tr>
<td>8</td>
<td>Importation &amp; Initiation</td>
<td>3W</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 to 6 weeks</td>
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</table>

Through the EMEA, there is a common framework for initiating clinical trials in EU Member States.
Voluntary Harmonisation Procedure

- Launched as a EU pilot project in February 2009
- Amended guidelines issued in March 2010
- Facilitates multinational Competant Authority (CA) submissions across the EU
- A coordinated assessment of an application for a clinical trial
- The trial must still be authorized at national level
- Consists of 3 phases
- Centralized assessment but not centralized approval
- Minimum Timeline: 45 days
- Maximum Timeline: 75 days*

* IF ASSESSMENT OF LOCAL DOCUMENTATION IS SATISFACTORY
Expected Approval Timelines ATMP

Regulatory Submissions - CA (VHP) / EC

- **DE:** 60 to 90 days
- **IT:** 50 to 60 days
- **NL:** 40 to 50 days
- **SE:** 60 to 70 days
- **ES:** VHP tbc; non ATMP
- **UK:** 30 to 60 days

*ES: VHP tbc; non ATMP
**UK: 30 to 60 days
***FR: 60 to 90 days
Clinical Development
Selection of Tumor

Tumor Selection

Many Types with Known Responsiveness to Immunotherapies

Solid Tumors

- Melanoma: IFN, IL-2, autologous LAK/TIL, anti-CTLA-4 (Yervoy)
- Renal cell: IL-2, autologous LAK/TIL
- Colon cancer: Levamisole
- Bladder cancer: BCG

Hematologic tumors

- NHL/CLL: Rituxan
- CML: Interferon alpha
Key Study Design Issues

- **Indication**
  - Tumor Stage
  - Treatment line

- **Regimen**
  - Single-agent
  - Combination

- **Randomization**
  - Non-randomized
  - Randomized

- **Control**
  - Placebo Control
  - Active Comparator

- **Endpoint**
  - TTP
  - PFS
  - DFS
  - OS
Definition of the Patient Population

Inclusion
- Early- vs. late-stage disease?
- Resectable tumor
- Histopathology
- Tumor genotype?
- Prior treatment?

Exclusion
- Poor functional status (ECOG >1)
- Prior immunotherapy
- Autoimmune diseases?
- Neutropenia
Randomized Trials in Phase II

**Design Phase 3 Study**
- Select measurable and clinically meaningful endpoint
- Define a clinically relevant risk
- Determine number of events based on 90% power

**Design Phase 2b Screening Study**
- Randomized, controlled design using the phase 3 study endpoint
- Determine number of events (approximately 25% of phase III)
- Determine threshold for phase 2 success, e.g. RR = 0.82

**Conduct Phase 2b Screening Study**
- Pre-determine decision-making criteria, e.g.
  - Observed RR > 0.82 → “no go”
  - Observed RR between 0.71 and 0.82 → further evaluation required
  - Observed RR < 0.71 → “clear signal, green light phase 3”
Endpoint Selection

### Overall Survival
- Rapid disease progression of pivotal study
- Requires less frequent subject visits meaning less complicated and costly studies
- Requires longer duration studies than PFS and other endpoints based on tumor size or progression
- In a pivotal study, OS provides a stronger basis for approval than PFS or TTP

### PFS/TTP/DFS
- Faster trial, especially good for slow disease progression or POC studies
- Imaging becomes pivotal thus greater cost associated with IAC, independent reads, and image management
- Imaging more frequent than SOC which means more expense and complexity for sites
- Immune recruitment to tumor sites can appear as progression under RECIST 1.1
Feasibility & Site Selection
Country selection based on a robust feasibility will provide the best chance of success for a trial where there is little precedent in most countries for anti-cancer vaccines.

Regulators outside the US may be unfamiliar and thus slower to approve trials with cell-based immunotherapy.

Exportation of tissue samples for vaccine production is highly regulated in certain countries.

Importation and customs delays can put vaccine shipments at risk.

Concentrating sites in emerging markets will hurt uptake at product launch because the complex nature of anti-cancer vaccines means that prescribers need significant experience during clinical trials to establish commercial use.
Site selection can include identification and evaluation of surgeons, pathologists, leukapherisis centers, and medical oncologists. Site-specific capabilities and regulations, e.g., dedicated glove box for adjuvants, e.g., BCG. OS trials following a series of inoculations tend to be easy for sites, opening up the possibility of community-based oncologists (e.g., CCOP) and central IRB sites.
Logistics, Operations, and CMC
Logistical and Operation Issues for Autologous Cell-Based Vaccines

**Production**
- Coordination between surgeons, pathologists, leukapherisis centers, and oncologists

**Shipping**
- Importation/export of tissue samples and cell-based therapy

**Administration**
- Intradermal injection training

**Tracking**
- Handling, processing, and shipping of tumor samples should comply with GMP and SOPs
**Chemistry, Manufacturing and Controls**

**Autologous product**
- Culture period < 1 wk
- <20 final product vials/lot
- No cryopreservation

- **Bulk**
  - Not performed

- **Final Release**
  - Gram stain and LAL
  - Pre-release
  - Sterility
    - 2 d read, pre-release
    - Final read, post-release

**Allogeneic product**
- Extensive culture period
- ~100 final product vials/lot
- Cryopreservation used

- **Bulk**
  - Sterility and LAL
  - Hold lot until all results available

- **Final Release**
  - Gram stain and LAL
  - Results pre-release
  - Sterility
    - Results post-release
Sterility Testing Failures

- Must define actions in procedures – including notifications, investigation, etc.
- Must perform susceptibility testing and report results to clinician

LAL Testing: False positives / Interference

- (1,3)-β-D glucan molecules; Found in cell walls of most yeasts, molds, culture media, cellulose filters, gloves, and uniforms
- High rates of invalid tests due to interference

Aseptic Processing: Media Fills

- Recommend completing in support of Phase II and later (earlier if high risk manipulations required)
Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines; Availability


Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Questions & Answers

Please submit your questions via the Q&A box on the left side of your screen

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