New developments in clinical vaccinations

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Charité Comprehensive Cancer Center
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Cancer vaccine development – clinical opportunities

- High-risk populations (BRCA, FAP)
- Carcinogenic infections (Hepatitis, HPV)
- Premalignant lesions (leukoplakia, MDS)

- Adjuvant treatment
- Metastatic disease
Hierarchy of tumor antigens

Relevance of antigen for cancer cell proliferation

- Gangliosides e.t.c.
- Tyrosinase MART-1
- MAGE
- WT1
- Bcr-abl

Mutation
Fusion-protein
Antigen presenting cell

effector cell

Tumor cell

Antigen

TCR

Afferent

Apoptosis
Chemotherapy
Radiotherapy
Necrosis

Efferent
Antigen presenting cell

TCR

Antigen

Tumor cell

effector cell

Stimulation (e.g. Interleukin-2)

afferent

efferent

TCR

TCR
Early clinical vaccine trials
Tumoral and Immunologic Response After Vaccination of Melanoma Patients With an ALVAC Virus Encoding MAGE Antigens Recognized by T Cells

Tumoral and Immunologic Response After Vaccination of Melanoma Patients With an ALVAC Virus Encoding

Results
Forty patients with advanced cancer were treated, including 37 melanoma patients. The vaccines were generally well tolerated with moderate adverse events, consisting mainly of transient inflammatory reactions at the virus injection sites. Among the 30 melanoma patients assessable for tumor response, a partial response was observed in one patient, and disease stabilization in two others. The remaining patients had progressive disease. Among the patients with stable or progressive disease, five showed evidence of tumor regression. A CTL response against the MAGE-3 vaccine antigen was detected in three of four patients with tumor regression, and in only one of 11 patients without regression.

Conclusion
Repeated vaccination with ALVAC miniMAGE-1/3 is associated with tumor regression and with a detectable CTL response in a minority of melanoma patients. There is a significant correlation between tumor regression and CTL response. The contribution of vaccine-induced CTL in the tumor regression process is discussed in view of the immunologic events that could be analyzed in detail in one patient.
Active immunization towards the MAGE-A3 antigen in patients with metastatic melanoma: four-year follow-up results from a randomized Phase II study (EORTC16032-18031)

WhJ Kruit, S Suciu, B Dreno, V Chiarion-Sileni, L Mortier, C Robert, M Maio, F Lehmann, V Brichard, A Spatz, A Eggermont and U Keilholz

Wim HJ Kruit, ASCO 2011, JCO 2013
On behalf of the study Investigators
Department of Internal Oncology, Erasmus Medical Center (Daniel den Hoed Cancer Center)
Rotterdam, Netherlands
Melanoma Phase II Trial - Study Design

Open, randomized, Phase II study NCT00086866
(EORTC study 16032-18031 – GSK 249553/008)

Metastatic Melanoma
• Unresectable stage III and stage IV M1a
• 1st line metastatic treatment
• Progressive disease
• MAGE-A3 (+) tumor

N = 34
MAGE-A3 + AS02\textsubscript{B}
• Cycle 1: q2w x 6
• Cycle 2: q3w x 6
• Cycle 3: q6w x 4
• Cycle 4: q3m x 4 - q6m x 4
• Total: 4 years

N = 34
MAGE-A3 + AS15

MAGE A3 rec. protein 300 ug i.m.
AS15 (MPL, QS21, CpG, liposome-based Adjuvant)
AS02\textsubscript{B} (MPL, QS21, o/w emulsion based Adjuvant)
Induction of anti-MAGE-A3 antibody response

- Immunological Adjuvant Systems are not equivalent

![Graph showing antibody titer over time for different adjuvants](image)
Induction of anti-MAGE-A3 CD4+ T-cells

RecMAGE-A3 + AS02B

Max Ratio baseline/any timepoint

CD4 + T cell Responders*

6/29
21%

RecMAGE-A3 + AS15

18/26
69%

*CD4 + T cell Responders are defined as when ratio any time point CD4 activity/ baseline CD4 activity is >4
Melanoma Trial - Clinical Results (1)

- **Immunological Adjuvants Systems are not equivalent**

- **Median follow-up = 4-Years**
  - N patients who have received > 16 doses:
    - recMAGE-A3 + AS15 Arm: 8 patients
    - recMAGE-A3 + AS02 Arm: 5 patients

- **5 clinically objective responses were observed**

<table>
<thead>
<tr>
<th></th>
<th>recMAGE-A3 + AS02</th>
<th>recMAGE-A3 + AS15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Duration</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>1</td>
<td>7 months</td>
</tr>
<tr>
<td>SD &gt; 16 wk</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>PD*</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>NE</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

- * MixR in 3 (AS02) and 4 (AS15) patients, respectively
- **CR**: Complete Response, **PR**: Partial Response, **SD**: Stable disease, **PD**: Progressive Disease, **NE**: Non evaluable
Overall Survival

Median survival (95%CI):
recMAGE-A3 + AS15 : 33.0 (18.6 - not reached) months
recMAGE-A3 + AS02B : 19.9 (14.5-25.4) months

Number of patients at risk : 21 36 24 19 16 8 2
                     29 36 25 13 8 3 0
Melanoma Trial - Conclusions

• Both MAGE-A3 ASCI formulations were well tolerated

• recMAGE-A3 + AS15 showed clinical activity in metastatic melanoma
  – 25% tumor control rate (CR+PR+SD)
  – 11% objective response rate (CR+PR)
  – Long-lasting responses and SD
  – A median survival of 33 months

• recMAGE-A3 + AS15 yielded high MAGE-A3-specific antibody titers and T-cell induction

• AS15 was selected for multiple Phase III developments
Hierarchy of tumor antigens

Cancer-specific antigen expression

Relevance of antigen for cancer cell proliferation

Gangliosides e.t.c.  Tyrosinase MART-1  MAGE

WT1  Bcr-abl

Mutation Fusion-protein
Cancer antigen pilot prioritization: representation of ranking based on predefined and preweighted criteria and subcriteria.

Criteria:
- specificity
- expression level
- patients with positive cancers
- stem cell expression
- oncogenicity
- cellular location of expression
- number of epitopes
- immunogenicity
- therapeutic function

WT1
MUC1
LMP2
HPV E6 E7
EGFRvIII
HER-2-neu
Idiotype
MAGE A3
p53 (non-mut.)
NY-ESO-1

Clinical efficacy of WT1 vaccine in active AML/MDS (modified IWG-assessment)

<table>
<thead>
<tr>
<th>Status at study onset</th>
<th>n</th>
<th>outcome</th>
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</thead>
<tbody>
<tr>
<td><strong>Untreated AML or sAML</strong></td>
<td>8</td>
<td>SD 2, 3, 3, 4, 4, 5, 7, 36+ months (4 pts. &gt; 50% blast reduction, 1 reduction of peripheral blasts, 1 erythoid response)</td>
</tr>
<tr>
<td>BM blasts med 70%, range 40 - 85%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RAEB I/II</strong></td>
<td>2</td>
<td>2 pts. with major neutrophil response (1 with 50% blast reduction), 6, 22 months</td>
</tr>
<tr>
<td><strong>No CR following chemo:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- PR</td>
<td>4</td>
<td>1 CR at week 10 for 12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 SD 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 PD</td>
</tr>
<tr>
<td>- no response</td>
<td>1</td>
<td>SD 7 mo with 50% blast reduction</td>
</tr>
<tr>
<td>- PD, relapse</td>
<td>3</td>
<td>1 SD for 2 mo, 2 PD</td>
</tr>
<tr>
<td></td>
<td><strong>18</strong></td>
<td>1 CR, 12 SD &gt; 2 months (6 patients &gt; 6 months)</td>
</tr>
</tbody>
</table>

Keilholz et al, BLOOD 2009
Clinical efficacy of WT1 vaccine in various carcinomas (RECIST 1.0)

<table>
<thead>
<tr>
<th>Tumor entity</th>
<th>n</th>
<th>Clinical response</th>
<th>WT1+T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian cancer (chemo-refractory x 2)</td>
<td>7</td>
<td>4 SD (6 - 27 months)</td>
<td>3 / 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 PD</td>
<td>2 / 3</td>
</tr>
<tr>
<td>Mesothelioma (chemo-refractory x 2)</td>
<td>4</td>
<td>2 SD (15 - 54+ months)</td>
<td>n.r.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 PD</td>
<td></td>
</tr>
<tr>
<td>Thyroid cancer (Iodine-refractory)</td>
<td>2</td>
<td>1 PR (10 months)</td>
<td>1 / 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 PD</td>
<td>0 / 1</td>
</tr>
<tr>
<td>Breast cancer (chemo-refractory x 2)</td>
<td>1</td>
<td>1 SPD (12 months)</td>
<td>1 / 1</td>
</tr>
<tr>
<td>Larynx cancer (chemo-refractory x 1)</td>
<td>1</td>
<td>1 PD</td>
<td>n.r.</td>
</tr>
<tr>
<td>Astrocytoma PD on RCT</td>
<td>1</td>
<td>1 SD (15 months)</td>
<td>n.r.</td>
</tr>
<tr>
<td>Gastric cancer (chemo-refractory x 1)</td>
<td>1</td>
<td>1 PD</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

Keilholz, Letsch et al, WT1 conference Kyoto, 2010
Immune-Resistance?

Blasts

Immune system

Effectors

Modulators

- TCR
- CD107
- Chemokine receptors
- Diff. Marker
- PD-1

MDSC

DC

- CTL
- T_H1
- T_reg
- TGF-β
- TGF-β, IL-10
- Chemokine receptors
- PD-1
- Diff. Marker
- CD107

T_reg
## Mechanism of resistance during WT1 vaccination

20 factors reported to correlate with primary or secondary resistance in cancer vaccine trials

<table>
<thead>
<tr>
<th>Leukemic blasts</th>
<th>T cells</th>
<th>Regulatory cells</th>
<th>B cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-loss/downregulation *</td>
<td>tetramer</td>
<td>regulatory T cells</td>
<td>Ig G</td>
</tr>
<tr>
<td>WT1-downregulation*</td>
<td>cytokines</td>
<td>Myeloid derived suppressor cells</td>
<td>Ig M</td>
</tr>
<tr>
<td>WT1-mutation *</td>
<td>CD137</td>
<td>-</td>
<td>(-)</td>
</tr>
<tr>
<td>TGF beta</td>
<td>CD107a</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IL-10</td>
<td>memory decrease</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PD-L1</td>
<td>PD-1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IDO</td>
<td>no BM homing#</td>
<td>-</td>
<td>Ig M</td>
</tr>
<tr>
<td>PI-9</td>
<td>HMOX</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Busse, J Transl Med 2010
# Ochsenreither, J Immunother 2011
Programmed Death 1 receptor (PD-1)

**Activation**
- T cells
- PD-1
- TCR
- S-Phase

**Exhaustion**
- T cells
- PD-1
- TCR
- Restricted Expansion

consecutive activation

functionality
High levels of PD-1 on CD8+ T cells at baseline associated with unfavorable clinical outcome.
Late clinical vaccine trials
The translational research cycle

Clinical trial → Modalities of clinical application → Basic research observation → Reasons for success or failure → Genomic alterations → Public and private antigens
Placebo-Controlled Phase III Trial of Immunologic Therapy with Sipuleucel-T (APC8015) in Patients with Metastatic, Asymptomatic Hormone Refractory Prostate Cancer


Fig 2. Primary end point, time to disease progression (intent-to-treat population). HR, hazard ratio.

Fig 3. Final overall survival (intent-to-treat population). HR, hazard ratio.
FDA OKs Provenge for Prostate Cancer Therapy

'Vaccine' Is an Immune Therapy That Treats Advanced Prostate Cancer

By Daniel J. DeNoon
WebMD Health News
Reviewed by Laura J. Martin, MD

WebMD News Archive

April 29, 2010 -- The FDA today approved Provenge, Dendreon Corp.'s individualized "vaccine" for the treatment of advanced prostate cancer.

The action comes more than three years after an FDA advisory panel recommended approval, declaring the immune therapy safe and effective. But FDA concerns over efficacy led the FDA to delay a decision until more data became available.
Adjuvant Ganglioside GM2-KLH/QS-21 Vaccination Versus Observation After Resection of Primary Tumor > 1.5 mm in Patients With Stage II Melanoma: Results of the EORTC 18961 Randomized Phase III Trial

Alexander M.M. Eggermont, Stefan Suciu, Piotr Rutkowski, Jeremy Marsden, Mario Santinami, Philippa Corrie, Steinar Aamdal, Paolo A. Asciero, Poulam M. Patel, Wim H. Kruit, Lars Bastholt, Lorenzo Borgognoni, Maria Grazia Bernengo, Neville Davidson, Larissa Polders, Michel Praet, and Alan Spatz
Fig 2. Results of second interim analysis. Kaplan-Meier curves of (A) relapse-free (hazard ratio [HR], 1.00; 98% CI, 0.75 to 1.34; two-sided Wald test $P = .99$) and (B) overall survival (HR, 1.66; 99.99% CI, 0.69 to 3.99; two-sided Wald test $P = .02$) from random assignment by treatment group. Cox models stratified by Breslow thickness, lymph node dissection, ulceration, and sex.

Fig 3. Results of final analysis. Kaplan-Meier curves of (A) relapse-free (hazard ratio [HR], 1.03; 95% CI, 0.84 to 1.25; two-sided Wald test $P = .81$) and (B) overall survival (HR, 1.16; 95% CI, 0.90 to 1.51; two-sided Wald test $P = .25$) from random assignment by treatment group. Cox models stratified by Breslow thickness, lymph node dissection, ulceration, and sex.
Merck KGaA ends lung cancer vaccine trials

FRANKFURT, Sept 12 Fri Sep 12, 2014 8:04am EDT

0 COMMENTS | Tweet | Share | Share this | Email | Print

(Reuters) - German drugmaker Merck KGaA drug stopped all remaining clinical studies of the experimental lung cancer vaccine tecemotide, formerly known as Stimuvax, after renewed attempts to show its effectiveness failed.

Press release Sept. 12, 2014
GSK cancer vaccine fails in lung cancer trial

WORLD NEWS | MARCH 20, 2014
KEVIN GROGAN

GlaxoSmithKline has suffered a setback after announcing more disappointing late-stage data from a non-small cell lung trial of its cancer vaccine MAGE-A3.

The UK major says that its MAGE-A3 antigen-specific cancer immunotherapeutic did not meet its first or second co-primary endpoint in a Phase III NSCLC trial. The study did not significantly extend disease-free survival when compared to placebo in the overall MAGE-A3 positive patients or patients who did not receive chemotherapy.

The MAGRIT trial enrolled 2,312 MAGE-A3-positive patients across more than 400 sites in 34 countries. Patients were given up to 13 intramuscular injections of either the immunotherapeutic or placebo over a period of 27 months.
GSK cancer vaccine fails first part of melanoma trial

WORLD NEWS | SEPTEMBER 05, 2013
KEVIN GROGAN

GlaxoSmithKline’s cancer vaccine has failed to meet its first co-primary endpoint in a Phase III melanoma clinical trial.

The drugs giant notes that an independent analysis of the DERMA study of its MAGE-A3 cancer immunotherapeutic showed that it did not significantly extend disease-free survival in stage IIIB/C melanoma patients with macroscopic nodal disease, whose tumours expressed the MAGE-A3 gene when compared to placebo. The aforementioned gene is expressed in about 65% of stage III melanomas.

Press release Sept. 5, 2013
Subgroup analysis still maturing
Vaccine

Antigen presenting cell

Antigen

effector cell

TCR

TCR

TCR

Antigen

Tumor cell

How to overcome low efficacy
Antigen presentation and T-cell stimulation:

- **Vaccine**: Introduction of antigen-presenting cells.
- **Antigen presenting cell**: Processes the vaccine and presents antigen.
- **Antigen**: Recognized by T-cell receptors (TCR).
- **Effector cell**: Activated by stimulation (e.g., Interleukin-2).
- **Stimulation (e.g., Interleukin-2)**: Ensures continuous T-cell activity.
- **Tumor cell**: Targeted for destruction by effector cells.
gp100 Peptide Vaccine and Interleukin-2 in Patients with Advanced Melanoma

Douglas J. Schwartzentruber, M.D., David H. Lawson, M.D., Jon M. Richards, M.D., Ph.D., Robert M. Conry, M.D., Donald M. Miller, M.D., Ph.D., Jonathan Treisman, M.D., Fawaz Gailani, M.D., Lee Riley, M.D., Ph.D., Kevin Conlon, M.D., Barbara Pockaj, M.D., Kari L. Kendra, M.D., Ph.D., Richard L. White, M.D., Rene Gonzalez, M.D., Timothy M. Kuzel, M.D., Brendan Curti, M.D., Phillip D. Leming, M.D., Eric D. Whitman, M.D., Jai Balkissoon, M.D., Douglas S. Reintgen, M.D., Howard Kaufman, M.D., Francesco M. Marincola, M.D., Maria J. Merino, M.D., Steven A. Rosenberg, M.D., Ph.D., Peter Choyke, M.D., Don Vena, B.S., and Patrick Hwu, M.D.
Schwartzentruber et al., NEJM 2011

B Overall Survival

![Graph showing overall survival for Interleukin-2 alone and Interleukin-2 + vaccine.](image)

- **Overall Survival (%)**
- **Years**

<table>
<thead>
<tr>
<th>Years</th>
<th>Interleukin-2 alone</th>
<th>Interleukin-2 + vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>54</td>
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<tr>
<td>3</td>
<td>26</td>
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<td>6</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

P = 0.06

**No. at Risk**
- Interleukin alone: 94, 46, 26, 14, 8, 4, 1
- Interleukin-2 + vaccine: 91, 54, 37, 20, 8, 4, 1
T-cell-Targets for immunoregulatory antibodies

I Mellman et al. Nature 480, 480-489 (2011)
Anti CTLA4

Antigen presenting cell

B7

CTLA4

Tumor cell

PD1

PD-L1

effector cell

CD28

Anti PD1/PDL1

efferent

afferent
Future direction
... leading into the presentation by Ignacio Melero