ESMO Preceptorship programme – Prague 2015

Immuno-Oncology and Prostate Cancer

Gero Kramer
Long way to Immunotherapy of Prostate Cancer

Timeline | Milestones in the development of active immunotherapy

- William Coley uses live bacteria as immune stimulant to treat cancer
- Discovery of molecularly defined tumour antigens recognized by human T cells
- First approval of therapeutic cancer vaccine
- Discovery of tumour-specific antigens in mice by George Klein
- First approval of monoclonal antibody as anti-cancer therapy
- Burnet proposes theory of immunosurveillance
- IL-2 approved as anti-cancer therapy
- Sir Mac Burnet publishes theory of acquired immunological tolerance
- Dendritic cells discovered by Ralph Steinman
- First report of complete/partial regressions with therapeutic cancer vaccine

IMMUNOTHERAPY IN CANCER

Breakthrough = Prostate Cancer

Big Surprise!
PROSTATE CANCER AS AN IDEAL MODEL FOR IMMUNE THERAPY
# High Prostate Cancer Rate at Autopsy

<table>
<thead>
<tr>
<th>Autopsy study</th>
<th>Sample size</th>
<th>Pca detection rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sakr et al.</td>
<td>249</td>
<td>24</td>
</tr>
<tr>
<td>Soos et al.</td>
<td>139</td>
<td>39</td>
</tr>
<tr>
<td>Zlotta et al.</td>
<td>320</td>
<td>37 vs 35</td>
</tr>
<tr>
<td>Haas et al.</td>
<td>164</td>
<td>43</td>
</tr>
<tr>
<td>Sanchez-Chapado et al.</td>
<td>162</td>
<td>19</td>
</tr>
<tr>
<td>Stamatiou et al.</td>
<td>212</td>
<td>19</td>
</tr>
</tbody>
</table>

Long Prostate Cancer-Continuum – Indolent Course of Disease

- PIN
- Organ confined
- Regional
- PSA failure
- Node +
- Castration-refractory
- Disseminated
- Immunological intervention

Prophylaxe
"THE HUMAN PROSTATE IS AN IMMUNOCOMPETENT SITE"

as it is exposed to regular contacts with antigens from the outside and forms a major immunological barrier that prevents break of immune tolerance against prostatic antigens

KRAMER et al., EUR UROL 51:1202, 2007
ADAPTIVE IMMUNITY - LYMPHOCYTES IN
NORMAL PROSTATE (18 - 25 YRS)

Cells/mm² (5 Pats)
CD3⁺ CD4⁺ CD8⁺
7±3 2±1 5±2

1-5% HLA-DR pos. glands

THEYER, KRAMER et al., Lab Invest 66:96, 1992
PROSTATE - A LYMPHATIC ORGAN (PALT)

Primary Lymphoid Follicle  
Secondary Lymphoid Follicle  
Lymphoid Aggregate

Di CARLO et al., PROSTATE 67:1070, 2007
Chronic intraprostatic leukocyte infiltration increases with age and prevalence of PC.
Is prostate cancer an immunologic/infectious disease?

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonorrhea</td>
<td>1.35</td>
</tr>
<tr>
<td>HPV</td>
<td>1.39</td>
</tr>
<tr>
<td>all STD</td>
<td>1.48</td>
</tr>
</tbody>
</table>

29 Studies, Medline 1966 – 2004
6,022 cases, 7,023 controls

Taylor et al, Family Med 37:506-12, 2005
Clinical experience with immunotherapy in prostate cancer
<table>
<thead>
<tr>
<th><strong>Sipuleucel-T</strong></th>
<th>Autologous cellular immune-therapy</th>
<th>Stimulates a T cell immune response against cancer cells (+ for PAP)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ipilimumab</strong></td>
<td>IgG1 Human monoclonal antibody</td>
<td>Blocks the activity of CTLA-4 and Treg expression</td>
</tr>
<tr>
<td><strong>Tasquimod</strong></td>
<td>Oral quinolone-3-carboxamide</td>
<td>Antitumor action by inhibition of angiogenesis / immunomodulation</td>
</tr>
<tr>
<td><strong>Prostvac-VF</strong></td>
<td>Vector based vaccing</td>
<td>Viral particles, vaccinia, and fowlpox that infect APC cells promoting an immune response against PSA expressing cells</td>
</tr>
<tr>
<td><strong>GVAX</strong></td>
<td>(GM-CSF) gene-transfected tumor cell vaccine</td>
<td>Evocation of strong immunoreaction by Ag expressed on human PC lines modified by GM-CSF</td>
</tr>
</tbody>
</table>

Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer

Philip W. Kantoff, M.D., Celestia S. Higano, M.D., Neal D. Shore, M.D., E. Roy Berger, M.D., Eric J. Small, M.D., David F. Penson, M.D., Charles H. Redfern, M.D., Anna C. Ferrari, M.D., Robert Dreicer, M.D., Robert B. Sims, M.D., Yi Xu, Ph.D., Mark W. Frohlich, M.D., and Paul F. Schellhammer, M.D., for the IMPACT Study Investigators*
Sipuleucel Immunotherapy = dendritic cell vaccine

Should activate CD4+ and CD8+ T-cells

Minimum of 50 million autologous CD54 + cells (T-cells, B-cells, APCs, eosinophiles)

Drake et al, NatureReviews/Immunology, 2010
Primary endpoint: Overall survival
Secondary endpoint: Time to objective disease progression
64% of patients in the control group, following progression, crossed over to receive autologous Immunotherapy made from cryopreserved cells.

Sipuleucel-T: Impact Phase 3 trial

4.1 month survival benefit

Reduction in risk of death:
22.5% HR = 0.775 (95% CI: 0.614, 0.979)
P=0.032

Impact trial – Overall survival benefit in all subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; Median</td>
<td></td>
</tr>
<tr>
<td>≤ Median</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
</tr>
<tr>
<td>Nonwhite</td>
<td></td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; Median</td>
<td></td>
</tr>
<tr>
<td>≤ Median</td>
<td></td>
</tr>
<tr>
<td><strong>Bisphosphonate use</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Primary Gleason grade</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 3</td>
<td></td>
</tr>
<tr>
<td>≥ 4</td>
<td></td>
</tr>
<tr>
<td><strong>Gleason score</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 7</td>
<td></td>
</tr>
<tr>
<td>≥ 8</td>
<td></td>
</tr>
<tr>
<td><strong>No. of bone metastases</strong></td>
<td></td>
</tr>
<tr>
<td>0–5</td>
<td></td>
</tr>
<tr>
<td>6–10</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td></td>
</tr>
<tr>
<td><strong>PSA level</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; Median</td>
<td></td>
</tr>
<tr>
<td>≤ Median</td>
<td></td>
</tr>
<tr>
<td><strong>LDH level</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; Median</td>
<td></td>
</tr>
<tr>
<td>≤ Median</td>
<td></td>
</tr>
<tr>
<td><strong>Alkaline phosphatase level</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; Median</td>
<td></td>
</tr>
<tr>
<td>≤ Median</td>
<td></td>
</tr>
</tbody>
</table>

CLINICAL RESPONSE AFTER SIPULEUCEL-T IN CRPC

- No difference in median time to objective disease progression (14.6 vs 14.4 weeks)
- No difference in median time to clinical disease progression
- Only one patient had partial objective response
- PSA reduction >50% in 8/311 (2.6%) pts after Sipuleucel-T vs 2/153 (1.3%) in placebo group

A Theoretical Mathematical Model of Differential Effects of Immunotherapy vs Chemotherapy

Changes in PSA values might not reflect treatment response to immunotherapy...
Sipuleucel-T has effect on quality of life and delayed time to opiat use

Opiat-free after 12 Months:
50.6% Sipu-T
43.1% Placebo

Median opiat-free time:
12.6 (Sipu) vs 9.7 (Pb) Mo
HR: 0.755; 95%
CI: 0.579-0.985; P=0.038)
## IMPACT STUDY

### Most common side effects (≥5%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sipuleucel-T</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated (N)</td>
<td>338</td>
<td>168</td>
</tr>
<tr>
<td>Chills</td>
<td>54</td>
<td>13</td>
</tr>
<tr>
<td>Fever</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>Headache</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Influenza like symptoms</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>

Mostly within 1 day of infusion, consistent with release of cytokines

Sipuleucel-T - Some additional facts

- Recently approved by EMEA for asympt./minimally symptomatic metastatic CRPC (non visceral)
- Ongoing European Study (Vienna, Nijmegen, London, Paris)

Mulders et al, Cancer Immunol Immunother, 2015
Sipuleucel-T in prostate cancer

Do immune response parameters work?

Some aspects to discuss!
### IMMUNE RESPONSE AFTER SIPULEUCEL-T

<table>
<thead>
<tr>
<th></th>
<th>Sipuleucel-T</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ab titers against PA2024 &gt;400</td>
<td>66%*</td>
<td>3%</td>
</tr>
<tr>
<td>Ab titers against PAP &gt;400</td>
<td>29%*</td>
<td>1%</td>
</tr>
<tr>
<td>T-cell proliferation response to PA2024</td>
<td>73%</td>
<td>12%</td>
</tr>
<tr>
<td>T-cell proliferation response to PAP</td>
<td>27%</td>
<td>8%</td>
</tr>
</tbody>
</table>

*Significant Association with longer survival (p<0.001 and p=0.08)

Sipuleucel-T immune parameters correlate with survival: an analysis of the randomized phase 3 clinical trials in men with castration-resistant prostate cancer

Nadeem A. Sheikh · Daniel Petrylak · Philip W. Kantoff · Corazon dela Rosa · Frances P. Stewart · Ling-Yu Kuan · James B. Whitmore · James B. Trager · Christian H. Poehlein · Mark W. Frohlich · David L. Urdal
Significant positive correlations between OS and cumulative (across the infusions) APC activation, APC count and total nucleated cell count *

* Remained after adjusting for baseline PSA and LDH
Activation of antigen-presenting cells increases until 3rd Vaccination*

*Prime-boost effect

Increased serum levels of T-cell activation-associated Cytokines
OS correlates with peripheral immune response against PA2024 or PAP after vaccination (humoral response)
Immune responses after Sipuleucel-T

Also post treatment antibody responses specific to PA2024 and PAP (isotype switching from IgM to IgG)

Epitope spreading – also effective against non target cancer antigens

Other questions?
  e.g. whether DCs release IL-12? Without IL-12 release no TH1 response and no activation of cytotoxic T cells”
Pretreatment frequency of circulating IL-17^+CD4^+ T-cells, but not Tregs, correlates with clinical response to whole-cell vaccination in prostate cancer patients

Evelyna Derhovanessian^1*, Victoria Adams^2, Karin Hähnel^1, Andrea Groeger^1, Hardev Pandha^3, Stephen Ward^2 and Graham Pawelec^1

^1Department of Internal Medicine II, Center for Medical Research, University of Tübingen, Tübingen, Germany
^2Onyx Ltd., London, United Kingdom
^3Department of Oncology, Postgraduate Medical School, University of Surrey, Guilford, United Kingdom
IL-17A IS OVEREXPRESSED IN BPH AND PROSTATE CANCER

- ONLY ACTIVATED BPH T-CELS EXPRESS IL-17A ABUNDANTLY
- IL-17A AUGMENTS PRODUCTION OF OTHER PROINFLAMMATORY CYTOKINES BY STROMAL CELLS (IL-6 13x; IL-8 26x)

Uncontrolled IL-17 immune response
Vaccination strategies less effective in the elderly! Aged-related impairments of the immune system

- Decreased thymic production of naive T cells\(^1\)

- Collapse in diversity of both naive and memory T cell subcompartments\(^2\)

- Decreased T cell responsiveness (\(\downarrow\) CD28 expression)\(^3\)

1 Aspinall et al, Immun Ageing., 4:9, 2007
Position of Sipuleucel-T in the natural course of PC?
Treatment Continuum in Advanced Prostate Cancer

- **Local therapy**
- **Castration-sensitive**
  - Asymptomatic
  - Mildly symptomatic
- **Castration-resistant**
  - Symptomatic

**ADT+Docetaxel**
- **Enzalutamide/Abiraterone**
- **Docetaxel**
- **Radium223**
- **Cabazitaxel**

**Secondary Hormonal Manipulations?**

*In Europa in Studien*

**Sipuleucel-T**
**Randomized phase II study of concurrent docetaxel plus vaccine vs vaccine alone in mCRPC**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Median time to progression (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine alone</td>
<td>14</td>
<td>1.8</td>
</tr>
<tr>
<td>Vaccine + Docetaxel</td>
<td>14</td>
<td>3.2</td>
</tr>
<tr>
<td>Docetaxel postprogression on vaccine</td>
<td>11</td>
<td>6.1</td>
</tr>
<tr>
<td>Docetaxel alone</td>
<td>25</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Vaccine can be given with chemo without compromising a T-cell specific response
Cumulative fold increase in APC activation (CD54) greater in earlier disease states (e.g. neoadjuvant)

What about very early Sipu-T and has Sipu-T also a local immune effect at tissue level?
Methods: Open-label phase II study, 37 untreated PC patients evaluable, Comparison of immune infiltrates in radical prostatectomy specimens (post-treatment) with pretreatment biopsies
Neoadjuvant Sipu-T: >3-fold increase in cytotoxic and helper T-cells

- T-cells PD-1, Ki-67 pos.
- Magnitude of circulating immune response did not directly correlate with T-cell infiltration in prostate

Similar observation with HIFU Treatment in prostate cancer

Heated stressed apoptotic CaP- cells are immunostimulatory

LOFU increase activation/delivery of immune effector cells to tumor sites by increased Ag shedding and disruption of tumor-induced biological barriers
Questions:

Recruitment of T-cells also in metastatic deposits in mCRPC patients?

Does it account role for OS seen with Sipu-T?
Also enhanced recruitment of T-cells to tumor site by blocking PD-1 or CTLA-4-signaling
Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial

Ipilimumab Phase III trial “043”

Post-docetaxel CRPC (N=799)

1:1

Patients stratified by investigator site, alkaline phosphatase, hemoglobin and ECOG PS

Single-dose bone-directed RT (8GY)

Ipilimumab (10 mg/kg)
WKS 1,4,7,10
Every 12 wks

Ipilimumab (10 mg/kg)
Every 12 wks

Placebo
WKS 1,4,7,10
Placebo
Every 12 wks

Treatment until disease progression or intolerable toxicity

Primary endpoint: Overall Survival (OS)
Secondary endpoint: Progression-free survival, safety
Exploratory endpoint: PSA response rate
### Ipilimumab post-docetaxel Phase III trial Results updated OS

<table>
<thead>
<tr>
<th></th>
<th>Ipi (n=399)</th>
<th>Pbo (n=400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% cl)</td>
<td>11.2 (9.6-12.6)</td>
<td>10.0 (8.4-11.2)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.84 (0.72-0.98)</td>
<td></td>
</tr>
<tr>
<td>Stratified log-rank *</td>
<td>P = 0.03</td>
<td></td>
</tr>
<tr>
<td>1-yr OS rate</td>
<td>47%</td>
<td>41%</td>
</tr>
<tr>
<td>2-yr OS rate</td>
<td>25%</td>
<td>17%</td>
</tr>
<tr>
<td>3-yr OS rate **</td>
<td>12%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Post-hoc subgroup analysis for pat with better prognostic profile: ALP<1.5 xULN, Hb >11g/dl, and no visceral mets:

Med. OS: 22.7 vs 15.8; HR (95% CI): 0.62 (0.45-0.86)
Another example to learn that a better understanding of mCRPC disease biology is necessary to transform the treatment of the diseases.
Tasquinimod – Oral therapy targeting tumor microenvironment

Gupta N. et al. Onco Targets Ther. 2014 Feb 12;7:223-34

Inhibiting regulatory myeloid cells and hypoxic response
Tasquinimod randomized Phase II

Anti-angiogenesis (VEGF-dependent and independent)
Immuno-modulation (Target: S100A9 protein)
n= 101 asymptomatic CRPC patients

Tasquinimod Phase III study in 1645 men

Key secondary endpoint: OS

Gupta N. et al. Onco Targets Ther. 2014 Feb 12;7:223-34
TASQUINIMOD PHASE 3 TRIAL SUMMARY

- Tasquinimod resulted in prolonged rPFS, 7 vs 4.4 months similar to phase 2

- Positive effect on rPFS did not translate into an improved OS (HR 1.097 [95% CI:0.938-1.282])

- In general, manageable safety similar to phase 2
TASQUINIMOD PHASE 3 TRIAL SUMMARY

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- Positive effect on rPFS did not translate into an improved OS (HR 1.097 [95% CI:0.938-1.282])

- In general, manageable safety similar to phase 2

Clinical development of TASQ in PC not being pursued

Carducci et al. ESMO 2015
Another promising candidate for a positive phase III Study

PROSTVAC VF VACCINE
Prostvac VF Vaccine as Antigen-Specific Immunotherapy

Viral vectors injected intradermally to infect and destroy EC

Drake et al, 2010
Prostvac in Patients with mCRPC (randomized Phase 2 study)

Asympt. Or minimally sympt. Metastatic CRPC N=125

PSA-TRICOM + GM-CSF n=84

Empty Vector + Placebo n=41

Progression:
- Treated at Physician Discretion
- Treated at Physician Discretion and/or salvage protocol

Survival

Primary endpoint: Progression Free Survival
Secondary endpoint: Overall Survival

Prostatic Recombinant viral vaccine
Prime: recombinant vaccinia virus expressing PSA in combination with B7.1, ICAM and LFA-3
virus expressing PSA in combination with B7.1, ICAM and LFA-3

Prostvac in pats with CRPC Phase 2: Efficacy

8.5 month survival benefit
Reduction in risk of death: 44%
HR: 0.56 (95% CL: 0.37-0.85)
P=0.0061

NS, not statistically significant

What are we waiting for?

Immunotherapy trials to come
Select ongoing immunotherapy trials in prostate cancer patients

### Ongoing checkpoint blockade trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Patient population</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>I/II</td>
<td>Chemotherapy naive mCRPC</td>
<td>Ipilimumab + abiraterone + prednisone</td>
</tr>
<tr>
<td>II</td>
<td>Metastatic castrate-sensitive prostate cancer</td>
<td>Ipilimumab + HT</td>
</tr>
<tr>
<td>I/II</td>
<td>Chemotherapy naive mCRPC</td>
<td>Ipilimumab</td>
</tr>
<tr>
<td>Iia</td>
<td>Localized prostate cancer</td>
<td>Neoadjuvant ipilimumab + HT followed by radical prostatectomy</td>
</tr>
<tr>
<td>III</td>
<td>Chemotherapy naive mCRPC</td>
<td>Ipilimumab vs. Placebo</td>
</tr>
</tbody>
</table>

Select ongoing immunotherapy trials in prostate cancer patients

Ongoing therapeutic vaccine trials (+ combination trials)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Patient population</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>I/II</td>
<td>High-risk men pre-prostatectomy</td>
<td>Neoadjuvant GVAX + cyclophosphamide (200 mg/m²) + HT vs. HT</td>
</tr>
<tr>
<td>III</td>
<td>Chemotherapy naive mCRPC</td>
<td>ProstVac-VF TRICOM + GM-CSF vs. ProstVac-VF TRICOM + placebo vs placebo + placebo</td>
</tr>
<tr>
<td>II</td>
<td>mCRPC</td>
<td>ProstVac-VF TRICOM + enzalutamide vs. enzalutamide</td>
</tr>
<tr>
<td>II</td>
<td>Chemotherapy naive mCRPC</td>
<td>ProstVac-VF TRICOM + docetaxel + prednisone vs. docetaxel + prednisone</td>
</tr>
<tr>
<td>II</td>
<td>Chemotherapy naive mCRPC</td>
<td>Sipuleucel-T vs. Sipuleucel-T + CT-011 (anti-PD1 antibody) vs. Sipuleucel-T + CT-011 + cyclophosphamide (125 or 250 mg/m²) CT-011 + cyclophosphamide (125 or 250 mg/m²)</td>
</tr>
<tr>
<td>I</td>
<td>Advanced Pca otherwise eligible to receive sipuleucel-T</td>
<td>Sipuleucel-T followed by ipilimumab</td>
</tr>
<tr>
<td>II</td>
<td>Chemotherapy naive mCRPC</td>
<td>Sipuleucel-T + immediate vs. delayed ipilimumab (3 weeks post-sipuleucel-T)</td>
</tr>
</tbody>
</table>
If PC is an infectious disease, possibilities for early interfering: prophylactic vaccination/effective early anti-infectious treatment

If we are late and chronic inflammation has already developed, we may stop or at least decelerate inflammation by anti-inflammatory modulation to prevent/delay cancer initiation

If chronic inflammation may have already triggered cancer, anti-inflammatory treatment may at least slow down PC progression
Immunotherapy for prostate cancer
My personal perspective

Potential to cure prostate cancer, but at an early setting and probably as part of combination therapy

Currently we lack enough knowledge of dysregulated immune system in prostate/metastatic deposits, which may interfere with efficacy of immunotherapy

Immunological and clinical monitoring will be a central issue and primary endpoint even more