There Are Newer and More Promising Agents Than Chemotherapy

Neal D. Shore

IPCU 2016
10% of pts recurrence

PCa Disease States - U.S. Statistics

Dx Pca
227,000 pts

High Risk* (PSA level, Gleason Score)
33,000 pts

Low Risk* (PSA level, Gleason Score)
187,000 pts

Metastatic Disease at Dx
7,000 pts

Radical Prostatectomy
45%
~99,000 pts

Radiation

Watchful Waiting or Alternative Therapy
25%
~55,000 pts

Biochemical Recurrence
~60,000 pts**

Within 10 years

Within 10 years

Radiation

(PSA level, Gleason Score)

30%
~66,000 pts

* Treatment and type of treatment rates same b/w High and Low risk.

** Used Midpoint of the % Recurrent ranges.

Datamonitor
PCa Disease States - U.S. Statistics

M0-CRPC: Nonmetastatic, castration-resistant

m0CRPC

M1-HSPC: Hormone-sensitive with evidence of distant metastases

m1HSPC

Metastatic Disease
~33,000 pts
Newly dxed - 7,000 pts
Recurring from BCR – 26,000 pts

High Risk (Gleason Score, PSADT) – high % progress to metastatic disease and median time to progression is ~2 years

Low Risk – less progress to metastatic disease and time to metastatic disease is 5-7 years

Biochemical Recurrence
~60,000 pts**

Datamonitor

The hypothesis

ADT: Androgen Deprivation Therapy; AR: androgen receptor

ADT

ADT + Docetaxel

AR-independent clones

AR-dependent clones
Chemo + ADT: Rationale behind the combination

**Pro**
- Attack de-novo testosterone independent clones early, allowing ADT to keep PrCa in remission longer
- Docetaxel may inhibit AR nuclear expression
- Some patients may be too frail for chemotherapy at progression.

**Con**
- ADT will take cells out of cycle and be less responsive to cytotoxics
- Some patients respond to ADT for a long time and never need chemotherapy

*Courtesy of C Sweeney*
Role of Tumor EMT in Metastasis and Therapeutic Resistance
The Future
“Tail of the Curve” Sets Immunotherapy Apart from Targeted Therapy

- I-O+I-O
- I-O+Targeted/Directed/SOC

Verdeil G. et.al. 2015 Biochimica et Biophysica Acta
Targeting T cells

The Cancer-Immunity Cycle

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)

Chen, D.S. and I. Mellman 2013
Immunity
Numerous Oncology Vaccines Being Developed in PCa

Vaccine Type
- Viral vector
- Bacterial vector
- Peptide
- Cell
- DNA
- RNA

Antigen
- PSA
- PSMA

Preclinical
- Aeterna Zentaris AEZS-120
- Oncbiomune PSA+ IL-2 + GM-CSF

Phase I
- Advaxis ADXS31-142
- Inovio INO-5150

Phase II
- CureVac CV-9104
- Bavarian Nordic ProstVac

Phase III
- Advantagene ProstAtak
## Vaccines are under investigation

<table>
<thead>
<tr>
<th>Brand (molecule)</th>
<th>Mechanism of Action</th>
<th>Company</th>
<th>Phase</th>
<th>Current Study/Existing Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostvac Subcutaneous inj.</td>
<td>PSA vaccine: Poxvirus express PSA + TRICOM (LFA-3, ICAM-1 and B7.1)</td>
<td>Bavarian Nordic</td>
<td>III</td>
<td>Phase III in mCRPC/ Phase II (N=125) showed successful OS as monotherapy in same population; Phase I combo with YERVOY showed long OS compared to historic controls</td>
</tr>
<tr>
<td>Prostatac(r)</td>
<td>PSA vaccine: transferrin transport technology</td>
<td>OncBio-Mune</td>
<td>IA/IB</td>
<td>BCR patients who have not started hormone therapy, N=48 / Phase I in 12 patients neo-adjuvant setting</td>
</tr>
<tr>
<td>CV9103/ CV9104</td>
<td>RNA Vaccine with 4 Antigens – PSA, PSCA, PSMA, STEAP1</td>
<td>CureVac</td>
<td>II</td>
<td>CV9104 in Phase II in mCRPC asymptomatic, N=197 patients/ Phase I in M0 CRPC, N=48, 80% of patients showed immune response and 2/3 responded to multiple antigens</td>
</tr>
<tr>
<td>ADXS31-142</td>
<td>PSA vaccine: Listeria monocytogenes-based vaccine</td>
<td>Advaxis</td>
<td>I/II</td>
<td>Phase I trial looking at safety of monotherapy and combination with pembrolizumab /Pre-clinical studies as monotherapy and combination</td>
</tr>
</tbody>
</table>

Source: Company websites and clinicaltrials.gov.
Inovio-On-going Phase I (PCa-001): PSA Relapse

- 6-month treatment at weeks of 0, 3, 12, 24
- 72-week follow-up
- 4 dose cohorts, total N=60

<table>
<thead>
<tr>
<th>Cohort</th>
<th>INO-5051 (mg)</th>
<th>INO-9012 (mg)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>B</td>
<td>8.5</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>D</td>
<td>8.5</td>
<td>1</td>
<td>15</td>
</tr>
</tbody>
</table>

DC = discharge; E = enrollment; S = screening; Wk = week.
The intervals between time points are not actually proportional.
Inovio-Phase I (PCa-002) Study

In patient with localized Pca under active surveillance (AS)

Subjects:
Low-intermediate risk PCa
Treatment naïve
No mets
Suitable for AS

Endpoints
Primary:
• Change in TIL

Secondary:
• PSA control
• DFS
• Time to new treatment

Biopsy at BL, Month6, M12 and M24

Monthly treatment x 4
Quarterly follow-up up to 2 years

• 4 treatments at a monthly basis
• PSA monthly x 6 months, then quarterly up to 24 months
• 2 year follow-up
• N=20-30 in single arm

The intervals between time points are not actually proportional.
Very High Risk and Oligo-Metastatic Prostate Cancer

- Uncertain standard of care
- Multiple advances:
  - Improved disease identification (imaging)
  - Improved surgical and radiation based treatments
  - Improved systemic therapies
- Multiple questions:
  - Best local primary treatment
  - Benefit of treatment to metastatic sites
  - Benefit of early intensification of systemic therapy
- Controlled clinical trials are critical
- At a minimum, these men should be captured in prospective registries (disease/QOL outcomes, bio-specimen collection)
Large Urology Group Practice Association-- LUGPA

• The LUGPA represents 121 large urology group practices
  – >2,000 physicians
  – >20% of the nation’s practicing urologists

• Committed to best practices, research, data collection and benchmarking to promote quality clinical outcomes
Objectives

• Review perspectives of PCF members and practitioners from large urology practice groups regarding management of contemporary very high risk localized, locally advanced, and oligo-metastatic prostate cancer
  – Gauge community practice trends towards the management of these men
  – Increase interaction between academics and community practices
  – Encourage LUGPA registries and clinical trials for these men
Design

• Data acquisition based on survey completed by 33 PCF meeting attendees and 39 members of large urology practice groups
  – Based on contemporary patients
  – Assessment of perspectives on
    • Local control
    • Use of systemic chemotherapy
    • Metastasis directed therapy
    • Perspectives on what we should focus on as a field

• Tremendous caveats – all acknowledged
Local Control

Use of Therapy to Primary

Percent

- VHR Localized
- Locally advanced
- Olgiometastatic

PCF | Community
Local Control

Type of Treatment to Primary -- PCF

Type of Treatment to Primary -- Community Practice

Percent

VHR Localized  Locally Advanced  Oligo-Metastatic

XRT  RP

Percent

VHR Localized  Locally Advanced  Oligo-Metastatic

XRT  RP
Use of Systemic Chemotherapy

Use of Docetaxel

- Adjuvant, PSA <0.1
- Adjuvant, PSA <1
- Adjuvant, PSA >1
- Oligo-Metastatic

Percent

PCF

Community
Use of Local Treatment To Metastatic Sites

SRT to Metastatic Site

Percent

PCF

Community
Future Areas of Focus

PCF
- Determine best local therapy (24%)
- Better imaging (24%)
- SRT to mets (24%)
- Immunotherapy (15%)
- Better ADT (12%)

Community Practice
- Determine best local therapy (26%)
- Immunotherapy (21%)
- SRT to mets (18%)
- Small molecule inhibitors (non-androgen) (15%)
- Better ADT (10%)
- Better imaging (10%)
Conclusions

• In these men where disease progression is highly likely, there is enthusiasm for aggressive disease control using local and systemic therapies
• Benefit of aggressive approaches is unclear
• With increased organizational structure to large community based practices comes opportunity for increased research and understanding
Combination Therapy Might Enhance Immunotherapy

Is combination a better approach to enhance immunotherapies?
Spectrum of Cancer Immunotherapies

- Recombinant Vaccines
- Cytokines / Immunocytokines
- Immune Checkpoint Inhibitors

Immuno-Oncology Platform: Combination Therapies

- Chemotherapy
- Radiation Therapy
- Small Molecule Targeted Therapies
  - Hormonal Therapy
Three Different Approaches Assessing Truncated AR

- Truncated AR have been linked to lack of response when treated with abiraterone or enzalutamide in the C-terminal loss of CRPC patients

<table>
<thead>
<tr>
<th>Assay Methodology</th>
<th>Assay Selective for AR-V7</th>
<th>Pt/Physician Experience</th>
<th>Bone Marrow Biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulating Tumor Cells</td>
<td>Johns Hopkins/AdnaGen</td>
<td>YES</td>
<td>Blood Draw</td>
</tr>
<tr>
<td></td>
<td>Memorial Sloan/Epic Sciences</td>
<td>IN PROGRESS</td>
<td>Blood Draw</td>
</tr>
<tr>
<td></td>
<td>MD Anderson</td>
<td>YES</td>
<td>Biopsy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Assay Methodology</th>
<th>AR and AR-V7 Detection</th>
<th>Assay Selective for AR-V7</th>
<th>Pt/Physician Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulating Tumor Cells</td>
<td>Johns Hopkins/AdnaGen</td>
<td>• Immunomagnetic isolation of CTCs - AR determination (AdnaTest ProstateCancerDetect kit (AdnaGen)) • AR-V7 determination, proprietary qRT-PCR assay (Johns Hopkins)</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>Memorial Sloan/Epic Sciences</td>
<td>• Immunofluorescence using N/C-terminal CTC Assay (IHC) to measure the existence of AR and C-terminal truncated AR splice variants</td>
<td>IN PROGRESS</td>
</tr>
<tr>
<td></td>
<td>MD Anderson</td>
<td>• IHC on formalin-fixed, paraffin-embedded sections of bone marrow specimens utilizing anti-AR N-terminal and anti-AR-V7 antibodies</td>
<td>YES</td>
</tr>
</tbody>
</table>
Hopkins Study: Current Oral Therapies Lack Activity in AR-V7+ Disease (cont’d)

- Only 1 AR-V7 positive patient showed any PSA reduction
- AR-V7 prevalence increased post additional treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline AR-V7+</th>
<th>AR-V7 status</th>
<th>PSA50</th>
<th>( P ) value</th>
<th>rPFS</th>
<th>( P ) value</th>
<th>OS (95% CI)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone (N=31)</td>
<td></td>
<td>+</td>
<td>0%</td>
<td>0.004</td>
<td>2.3 mos</td>
<td>&lt;0.001</td>
<td>11.1 mos (8.5–NR)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>–</td>
<td>68%</td>
<td></td>
<td>&gt;6.3 mos</td>
<td></td>
<td>NR (&gt;18 mos)</td>
<td></td>
</tr>
<tr>
<td>Enzalutamide (N=31)</td>
<td></td>
<td>+</td>
<td>0%</td>
<td>0.004</td>
<td>2.1 mos</td>
<td>&lt;0.001</td>
<td>7.4 mos (3.9–NR)</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td></td>
<td>–</td>
<td>53%</td>
<td></td>
<td>6.1 mos</td>
<td></td>
<td>16.0 mos (14.2–NR)</td>
<td></td>
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</table>

CI, confidence interval; rPFS, radiographic progression-free survival.

Galeterone: Combination of 3 Distinct Mechanisms of Action

First in Class Potential

**Androgen Receptor (AR) Degrader**
- Decreases AR Levels
- Differentiated Mechanism

**CYP17 Inhibitor**
- Inhibits Androgen Synthesis
- Validated Mechanism

**AR Antagonist**
- Blocks Androgen Binding
- Validated Mechanism

**GALETHERONE**

Active in CRPC patients and supporting data in patients with C-terminal Loss

No Steroids required

No Seizures to date
- Not a GABA<sub>α</sub> antagonist

Taplin et al. *Activity of Galeterone in Castrate-Resistant Prostate Cancer; EORTC-NCI-AACR Symposium Molecular Targets and Cancer Therapeutics*, 2014
Kwegyir-Afful AK et al. *Oncotarget* [published online July 14, 2015].
Tokai Research Reports (TK-001, TK-002).
Galeterone: Selective, Multi-targeted, Small Molecule for Treatment of CRPC

CYP17 Lyase Inhibitor
- Inhibits androgen synthesis

AR Antagonist
- Blocks androgen binding

AR Degrader
- Decreases AR levels

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<tr>
<th></th>
<th>CYP17 Lyase Inhibitor</th>
<th>AR Antagonist</th>
<th>AR Degrader</th>
</tr>
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<tbody>
<tr>
<td><strong>Abiraterone</strong></td>
<td>![Checkmark]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Enzalutamide</strong></td>
<td></td>
<td>![Checkmark]</td>
<td></td>
</tr>
<tr>
<td><strong>Galeterone</strong></td>
<td></td>
<td></td>
<td>![Checkmark]</td>
</tr>
<tr>
<td>- No mandatory steroids</td>
<td></td>
<td>- Not a GABA&lt;sub&gt;A&lt;/sub&gt; antagonist</td>
<td>- Active in C-terminal loss AR splice variants</td>
</tr>
<tr>
<td>- Fasting not required</td>
<td></td>
<td>- No seizures</td>
<td></td>
</tr>
<tr>
<td>- Preclinical activity in mutation T878A</td>
<td></td>
<td>- Preclinical activity in mutation F876L</td>
<td></td>
</tr>
</tbody>
</table>
ARMOR3-SV: First Precision Medicine

Prostate Cancer Pivotal Trial

Unique trial design finalized in consultation with FDA and EMA

Key Inclusion:
- Progressive metastatic (M1) disease on androgen deprivation therapy based on PCWG2
- Detectable AR-V7 from CTCs
- ECOG 0 or 1

Key Exclusion:
- Prior treatment with second generation antiandrogens (eg, abiraterone, enzalutamide)
- Prior treatment with chemotherapy for CRPC

Randomize 1:1 N=148

Galeterone 2550 mg/day

Primary Endpoint:
- Radiographic progression free survival (rPFS)

Secondary Endpoints:
- Time to cytotoxic therapy
- OS

Enzalutamide 160 mg/day

Taplin et al. Androgen Receptor Modulation Optimized for Response: Splice Variant (ARMOR3-SV); ASCO 2015
**Key Inclusion Criteria**
- M1 disease
- Progressive disease on androgen deprivation therapy based on PCWG2
- Detectable AR-V7 from CTCs
- ECOG 0 or 1

**Key Exclusion Criteria**
- Prior treatment with second generation antiandrogens (abiraterone, enzalutamide)
- Prior treatment with chemotherapy for CRPC

**Primary Endpoint**
- Radiographic progression free survival

**Secondary Endpoints**
- Overall Survival
- Skeletal related events
- Time to cytotoxic therapy

**Other Endpoints**
- Safety
- PSA50
- Time to progression and ECOG deterioration
- Best overall response by RECIST 1.1
- CTC characterization
- Pharmacokinetics
- Quality of life

**Randomize**
- Galeterone 2550 mg/day
- Enzalutamide 160 mg/day

**N<170**

- Independent Data Monitoring Committee planned
VIABLE
A Randomized, Double Blind, Multicenter, Parallel-Group, Phase III Study to Evaluate Efficacy and Safety of DCVAC/PCa versus Placebo in Men with Metastatic Castration Resistant Prostate Cancer Eligible for 1st Line Chemotherapy.
Introduction of DCVAC/PCa

SOTIO’s lead product is Active Cellular Immunotherapy for patients with prostate cancer, entitled DCVAC/PCa

**About the product**
- SOTIO’s prostate cancer immunotherapy treatment DCVAC/PCa is an autologous immunotherapy manufactured from the patient’s own white blood cells collected during leukapheresis procedure (1) at the apheresis center.

**Manufacturing**
- After leukapheresis, the harvested cells are sent to SOTIO’s GMP certified laboratories where they are processed into the DCVAC immunotherapy.
- Monocytes separated from the entire leukapheresis product (2) are cultivated *ex vivo* into immature dendritic cells (3). These immature dendritic cells are then pulsed with tumor cells killed by immunogenic cell death (4) using proprietary high hydrostatic pressure (HHP) technology. Subsequently, pulsed dendritic cells are matured (5) and the resulting product is frozen, stored in liquid nitrogen and shipped to the treatment site (6).

**Treatment**
- The first dose of the treatment is available for administration to the patient approximately four weeks after leukapheresis. A single leukapheresis session yields multiple doses (up to 15 doses) of DCVAC, which is sufficient to treat the patient for up to a year or more.
- After being thawed and diluted, the ACI is administered subcutaneously at regular treatment intervals (every 2-6 weeks) depending on the trial design.
- Following subcutaneous administration, dendritic cells migrate into lymph nodes. There they meet and activate *naïve* T-lymphocytes which allows them to recognize tumor antigens.
- *Naïve* lymphocytes become effector lymphocytes which rapidly proliferate. Anti-tumor specific T cells migrate via bloodstream through the entire body, searching for and destroying tumor cells.

**Clinical trials**
- Since 2012 SOTIO has launched five Phase II clinical trials with DCVAC/PCa. SOTIO’s global Phase III VIABLE study, was launched in May 2014 and is recruiting ~ 1200 patients in over 20 countries in Europe and USA.
DCVAC/PCa – Prostate cancer

Design of the global Phase III trial

- **Screening**
  - Day 0
  - Leukapheresis

- **Randomization**
  - DCVAC/PCa Manufacturing
  - DCVAC/PCa - up to 15 doses
  - N = 781
  - DCVAC/PCa + docetaxel
  - DCVAC/Pca boosting
  - 2:1 ratio
  - N = 389
  - Placebo + docetaxel
  - Placebo “boosting”

- **Follow-up…**
  - End of Treatment
  - Overall survival
  - 2nd line treatments

- **End of Study**

- **n=1170;** Primary Analysis at 657 deaths
  - Study duration – 40 months

Source: SOTIO

SOTIO Presentation_October 2015
Design of SP005

- **Screening**
- **Randomization**
  - 2:1 ratio
  - N = 781
  - DCVAC/PCa + docetaxel
  - Placebo + docetaxel
- **Leukapheresis**
- **DCVAC/PCa Manufacturing**
- **DCVAC/PCa up to 15 doses**
- **End of Treatment**
- **Follow-up...**
- **End of Study**

- **N = 389**
- Placebo boosting
- DCVAC/PCa boosting
- 2nd line Treatments
- OS

- **Enrollment:** 18 months
- **Study Duration:** 40 months
- **n=1170**
- 657 deaths (trial stops)

**New Stratification factors:**
- Region
- Prior therapy
- ECOG score

**P = 80%,**
5% significance
HR: 0.792
VIABLE: Study Phases

1) PRE-TREATMENT PERIOD
   • Screening (up to 28 days)
   • Randomization (IVRS or IWRS) 2:1 randomization ratio
   • Leukapheresis: within 14 days from randomization

2) CONCURRENT TREATMENT PERIOD
   • Standard of Care chemotherapy (docetaxel 75mg/m² + prednisone 5mg/m² bid, D1) q3w
   • The chemotherapy starts within 7 days after Leukapheresis and the 1st dose of the vaccine starts in Cycle 2
   • DCVAC/PCa q3w

3) MAINTENANCE BOOSTING PERIOD
   - After completion of 1st line standard of care for any reason, patient will continue on DCVAC or placebo until completion, refusal, intolerance or introduction of second line.

4) FOLLOW-UP PERIOD
   • After completing DCVAC doses, all patients will be followed until refusal, death or study closure upon reaching targeted number of events
   • Second line anti-tumor therapies under investigator’s discretion (based on the list of allowed therapies per protocol)
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   After completing DCVAC doses, all patients will be followed until refusal,
death or study closure upon reaching targeted number of events
Second line anti-tumor therapies under investigator´s discretion (based
on the list of allowed therapies per protocol)
STAMPEDE: Patient eligibility

High-risk, newly diagnosed, non-metastatic, node-negative

OR

Newly diagnosed metastatic or node-positive disease

OR

Previously treated with radical surgery and/or RT, now relapsing
STAMPEDE (UK): Trial design

Patients eligible for STAMPEDE >6500 recruited

Newly diagnosed M1 patients

All other patients

Randomization

**A** | ADT
---|---
**B** | Arm A + ZA
**C** | Arm A + DOC
**F** | Arm A + ZA + DOC
**G** | Arm A + ABI
**H** | Arm A + RT to prostate

**A** | ADT (+RT if N0 M0)
---|---
**B** | Arm A + ZA
**C** | Arm A + DOC
**F** | Arm A + ZA + DOC
**G** | Arm A + ABI

1Except patients with contraindication to RT
2Locally advanced (either node positive, or with 2 of 3 risk factors: stage T3/4, PSA ≥40ng/ml or Gleason sum score 8–10)

Parker CC et al. BJU Int 2013;111:697–9 (NCT00268476)

ADT: Androgen Deprivation Therapy; ZA: Zoledronic acid; DOC: docetaxel; RT: radiotherapy
Celecoxib with or without zoledronic acid for hormone-naïve prostate cancer: Results from STAMPEDE

Conclusions:
- Adding ZA does not improve FFS or OS
- Adding Cel does not improve FFS or OS
- Adding Cel+ZA does not improve FFS or OS in whole trial population
- However, adding Cel+ZA improves FFS and OS in M1
- Point estimate in M1 disease similar to adding docetaxel

Summary: OS

Summary: FFS
Newer Therapeutic Possibilities

• High risk localized(A)- BCR(B)-ASMC(C)-CRPC(D)

• (A)Androgen Annihilation/Intervention
• (B)Immunotherapy +/- ADT
• (C &D)Advanced Disease: Chemhormonal-Chemoimmunologic-Targeted/Selected Combinations
Thank You