Understanding the Current Prostate Cancer Treatment Paradigm

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An overview of major changes in prostate cancer care since 2010…

- Hormone therapies
- Chemotherapies
- Immunotherapy
- Radiation therapy

Outstanding questions
Treatment of prostate cancer 2009

Localized cancer

Recurrent or metastatic cancer

Surgery or radiation

Castration (ADT)

Castration-sensitive

Secondary Hormone Rx

Highly variable

Castration-resistant

Docetaxel
Treatment of prostate cancer 2017

Localized cancer

- Castration (ADT)
- Surgery or radiation

Recurrent or metastatic cancer

- Castration-resistant
- Castration-sensitive

Localized cancer:
- Castration (ADT)
- Surgery or radiation

Recurrent or metastatic cancer:
- Abiraterone
- Cabazitaxel
- Enzalutamide
- Docetaxel
- Radium-223
- Sipuleucel-T

Castration-sensitive:
- Abiraterone
- Enzalutamide

2010–2014:
- Docetaxel
- Salvage RT + hormones

2014–2017:
- Docetaxel
- Abiraterone
- Enzalutamide

2017:
FDA-approved drugs for mCRPC, 2010-2014

**Improved Overall Survival**

- 4/29/10: sipuleucel-T
- 6/17/10: cabazitaxel (post-docetaxel)
- 4/28/11: abiraterone (post-docetaxel)
- 8/31/12: enzalutamide (post-docetaxel)
- 12/10/12: abiraterone (pre-docetaxel)
- 5/15/13: radium-223 dichloride
- 9/10/14: enzalutamide (pre-docetaxel)

**Supportive Care**

- 11/18/10: denosumab (for prevention of skeletal problems)
- 9/19/11: denosumab (for fracture prevention)
First, some basics: Understanding the data: Things we care about in clinical trials

Number of patients

What is the “treatment arm” compared against (“control arm”)?

Was there adequate follow-up?

Were any findings statistically significant?
Understanding the data: “Survival curves”
(Also called the Kaplan-Meier curve)
And some way-way-way-way-background:
Castration stops testosterone stimulation of prostate cancer via the androgen receptor (AR)

Nobel Prize in Physiology or Medicine, 1966
“for his discoveries concerning hormonal treatment of prostatic cancer”

Charles Huggins, M.D. (1901 – 1997)


Source: www.Nobelprize.org
Androgen deprivation therapy (ADT) = castration therapy

- Goal: lower testosterone (T) to castrate levels
- Surgical castration (bilateral orchiectomy)
- Medical castration
  - GnRH agonists (leuprolide, goserelin, triptorelin, buserelin, histrelin)
  - GnRH antagonist (degarelix)
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Highly variable

Time

Tumor Burden / PSA
Recurrent prostate cancer after prostatectomy

A detectable level of PSA indicates persistence or recurrence of prostate cancer

Some men may be cured with “salvage radiation therapy”

RTOG 9601 asked whether anti-androgen therapy could improve outcomes (cancer control, overall survival) when added to radiation therapy
Bicalutamide + RT: better outcomes

A. Overall Survival, All Patients

- Placebo Group: 131 deaths
- Bicalutamide Group: 108 deaths

No. of Deaths

- Hazard ratio, 0.77 (95% CI, 0.59–0.99)
- P=0.04

Patients Who Survived (%)

Years since Randomization

B. Metastatic Prostate Cancer

- Placebo Group: 93 patients with treatment failure
- Bicalutamide Group: 63 patients with treatment failure

No. of Patients with Treatment Failure

- Hazard ratio, 0.63 (95% CI, 0.46–0.87)
- P=0.005

Patients with Metastatic Prostate Cancer (%)

Years since Randomization

12y: 76% vs 71% alive

12y: 14.5% vs 23% with metastasis

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Tumor Burden / PSA

Time

Tumor Burden

- Localized cancer
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  - Castration-resistant

- Recurrent or metastatic cancer
  - Recurrent or metastatic cancer
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  - Salvage RT + hormones
  - Abiraterone
  - Secondary Hormone Rx
  - Highly variable
  - Docetaxel

Abiraterone
Newly diagnosed metastatic prostate cancer

ADT has been the standard approach

In 2004, docetaxel was FDA-approved for *castration-resistant* disease due to 2 studies that demonstrated a benefit in overall survival


Shortly thereafter, investigators tried giving docetaxel to newly-diagnosed, *castration-sensitive* prostate cancer patients

![Graph showing survival rates](image)
What about earlier use of docetaxel in metastatic castration-sensitive prostate cancer?

Pros

- Attack testosterone-independent clones early
- Might allow ADT to keep disease in remission for longer period of time
- Some patients at the time of progression are too frail for chemo

Cons

- ADT may take cells out of cycle, making them less responsive to cytotoxics
- Some patients response to ADT for a long time and never need chemotherapy (overtreatment)
The New England Journal of Medicine

Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Christopher J. Sweeney, M.B., B.S., Yu-Hui Chen, M.S., M.P.H., Michael Carducci, M.D., Glenn Liu, M.D., David F. Jarrard, M.D., Mario Eisenberger, M.D., Yu-Ning Wong, M.D., M.S.C.E., Noah Hahn, M.D., Manish Kohli, M.D., Matthew M. Cooney, M.D., Robert Dreicer, M.D., Nicholas J. Vogelzang, M.D., Joel Picus, M.D., Daniel Shevlin, M.D., Maha Hussain, M.B., Ch.B., Jorge A. Garcia, M.D., and Robert S. DiPaola, M.D.

Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial


CHAARTED primary endpoint: Overall Survival

2017: LATITUDE and STAMPEDE

**Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer**

Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D., Nobuaki Matsubara, M.D., Alfredo Rodriguez-Antolin, M.D., Ph.D., Boris Y. Alekseev, M.D., Mustafa Özgüröglu, M.D., Dingwei Ye, M.D., Susan Feyerabend, M.D., Andrew Protheroe, M.D., Ph.D., Peter De Porre, M.D., Thian Kheoh, Ph.D., Youn C. Park, Ph.D., Mary B. Todd, D.O., and Kim N. Chi, M.D., for the LATITUDE Investigators*

**Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy**


Abiraterone studies: primary endpoint: Overall Survival

**LATITUDE**

- Hazard ratio, 0.62 (95% CI, 0.51–0.76)
- P < 0.001
- Overall Survival (%)
- Months: 0 to 42
- No. at Risk
  - Abiraterone: 597, 565, 529, 479, 388, 233, 93, 9
  - Placebo: 602, 564, 504, 432, 332, 172, 57, 2

**34.7 months vs not reached**

**STAMPEDE**

- Overall Survival in Patients with Metastatic Disease
- Probability of Overall Survival
- Months since Randomization
- No. of Patients (no. of deaths)
  - Combination therapy: 500 (22), 469 (50), 415 (57), 256 (18), 81
  - ADT alone: 502 (35), 460 (80), 371 (73), 215 (23), 60

**References**

Treatment of prostate cancer 2017

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Tumor Burden / PSA

Time

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Docetaxel

Abiraterone

Salvage RT + hormones

Highly variable

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Enzalutamide

Sipuleucel-T

Secondary

Abiraterone

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Radium-223

Cabazitaxel

Abiraterone

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Overall survival curves

**Sipuleucel-T**
- 25.8 mos
- 21.7 mos
- \( p = 0.03 \)

**Cabazitaxel**
- 15.1 mos
- 12.7 mos
- \( p < 0.0001 \)

**Abiraterone post-docetaxel**
- 14.8 mos
- 10.9 mos
- \( p < 0.001 \)

**Abiraterone pre-docetaxel**
- 34.7 mos
- 30.3 mos

**Enzalutamide pre-docetaxel**
- Hazard ratio, 0.71 (95% CI, 0.60–0.84)
- 32.4 mos
- 30.2 mos
- 29% reduction in risk of death

**Radium-223**
- Median overall survival, 14.9 mos
- Overall Survival
Sipuleucel-T (Provenge)

A vaccine delivered via intravenous infusion

Mechanism / logistics:

• “Autologous active cell immunotherapy”: a patient’s own blood cells are removed, “activated” with a protein (PA2024, prostatic acid phosphatase fused to GM-CSF), and re-infused

• Requires 3 rounds of pheresis and re-infusion 3 days later

An intravenous chemotherapy like docetaxel

Mechanism: interferes with cell division, but may be less likely to be pumped out of cancer cells than docetaxel

Phase III trial design
- Patients who have progressed on docetaxel therapy
Why bother with hormone therapies if the disease is “castration resistant”?

Mechanisms of resistance to hormone therapy

• Androgen production from non-testicular sources
  – Adrenal glands
  – Tumor cells themselves

• AR gene mutations (18-50%)

• AR gene amplification (up to 30%)

• Other ways to activate the AR without testosterone (ligand-independent)
Abiraterone acetate (Zytiga)

Oral medication, taken daily, with prednisone (steroid)

Mechanism:

- A steroidogenesis inhibitor
- Irreversible inhibitor of 17α-hydroxylase and C17,20-lyase CYP17 activity, two enzymes that are important for testosterone production in the adrenal glands
Enzalutamide (Xtandi)

Oral medication, taken daily

Mechanism of action

- An anti-androgen
- Competes for androgen binding to AR
- Inhibits AR translocation to the nucleus
- Inhibits binding to DNA
Radium-223 dichloride (Xofigo)

An intravenous radiation treatment

Mechanism

- A radioisotope containing an $\alpha$-emitting nuclide
- Targets bone metastases with high-energy $\alpha$ radiation of extremely short range that spares bone marrow, limiting toxic effects
- For patients with bone-only or bone-dominant disease

Logistics: monthly infusions x 6 months
Overall survival curves

**Sipuleucel-T**
- Overall survival: 25.8 mos
- Placebo: 21.7 mos
- \( p = 0.03 \)

**Cabazitaxel**
- Overall survival: 15.4 mos
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- Placebo: 30.3 mos

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- Placebo: 30.2 mos

**Radium-223**
- Overall survival: 30.2 mos
- Placebo: 29% reduction in risk of death

References:
## mCRPC and overall survival

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<th>N</th>
<th>OS</th>
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<td>Placebo</td>
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<td>13.6mo</td>
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Treatment of prostate cancer 2017

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Enzalutamide

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Sipuleucel-T

Abiraterone

Enzalutamide

Docetaxel

Cabazitaxel

Enzalutamide

Radium-223
Despite all the progress, there’s work to be done

**Outstanding questions**

- With so many drugs, what is the optimal sequence?
- What do we know about resistance to therapies?
- Can we identify cellular changes (genetic or other) that may explain more aggressive cancer behavior in black patients?
- What is the role for immunotherapy? Who benefits?

**Outstanding needs**

- Predictive biomarkers for aggressive disease, treatment response, intermediate endpoints
- New imaging techniques
One example of a potential biomarker that could tell us about treatment response and aggressive behavior

- **AR-V7** mRNA splice variant:
  - Missing Ligand Binding Domain (LBD)
  - Constitutively active
  - Associated with resistance to abiraterone and enzalutamide in mCRPC

**AR**: Xq11-12

**AR-V7**

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**Figure 2.** Waterfall Plots of Best Prostate-Specific Antigen (PSA) Response According to AR-V7 Status.

Panel A shows the 31 enzalutamide-treated patients, and Panel B the abiraterone-treated patients. The dotted line shows the threshold foring a PSA response (≥50% reduction in PSA level from baseline). Arrows indicate an increase of more than 100% in best PSA response. Daggers indicate patients in the enzalutamide cohort who had previously received abiraterone and patients in the abiraterone cohort who had previously received enzalutamide.

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RNA in situ hybridization (RNA ISH)

- Note: Need 20mer probes across transcript with 500-1000 base pairs of unique target (not possible for AR^{v567es})
- Cell line controls:
  (+) VCAP, 22Rv1
  (-) RWPE-1, PC3

Pre-treatment prostate: 1+ (Gleason 4+5)

During ADT Bladder TUR: 2+

Autopsy lung 2+ adrenal 2+ soft tissue 3+

AR-V7 RNA ISH, 40X  H&E, 20X

Results for metastatic castration-sensitive prostate cancer cohort

- AR-V7 detectable in some patients in both groups
  - “Brief response”: 6/9
  - “Sustained response”: 4/13

- Prognostic:

OS: NR vs 33 mo; $p=0.044$

PFS: 94 vs. 6.5 mo; $p=0.055$

RNA ISH: Conclusions / Other directions

- Automated RNA-ISH assay is feasible
- Archival FFPE prostate cancer tissue can be used to assess AR-V7 RNA
- Institutional cohort suggests baseline AR-V7 by this method is a *negative* prognostic marker
- Validation in larger cohorts is needed

- Other directions?

Archival Cohorts

- “Low clinical likelihood”
  - Gleason 6 prostatectomy (n=10)
  - Also: Gleason 7 and ≥8 (n=10 each)

- “High clinical likelihood”
  - mCRPC after multiple lines of therapy (n=12)
  - Castration-sensitive metastatic prostate cancer (ADT)
    - “Sustained response” (> 2.5 years; n=13)
    - “Brief response” (< 9 months; n=9)

Ongoing collaboration

MGH Cancer Center
- Phil Saylor
- Rick Lee
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- David Ting
- Kara Olivier
- Erika Meneely

MGH Pathology
- Chin-Lee Wu
- Kshitij Arora
- Rong Hu
- Vikram Deshpande
- Miguel Rivera

BMC
- Rawad Elias
- Gretchen Gignac
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