Evolving Uses of Androgen Deprivation Therapy (ADT) in Prostate Cancer Management

James Mohler, MD
Roswell Park Cancer Institute

America

• More is better, but perfect is the enemy of good
• New is better, but not always
• High tech is better, but low tech often works fine
• Expensive things are better, since they cost more but .....
Every 2 Minutes an American is Diagnosed with Prostate Cancer

Every 18 Minutes an American Dies of Prostate Cancer

How is ADT like a Volkswagen?

ADT = Androgen deprivation therapy
### VW has evolved ...

### And so has ADT!

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogens</td>
<td>DES parenteral</td>
</tr>
<tr>
<td>LHRH Agonists</td>
<td>leuprolide acetate, goserelin acetate, histrelin acetate, triptorelin pamoate</td>
</tr>
<tr>
<td>LHRH Antagonists</td>
<td>degarelix acetate</td>
</tr>
<tr>
<td>Anti-androgens</td>
<td>flutamide, bicalutamide, nilutamide, enzalutamide (MDV3100), *ARN509 (apalutamide)</td>
</tr>
<tr>
<td>5α-reductase inhibitors</td>
<td>finasteride, dutasteride</td>
</tr>
<tr>
<td>CYP17 inhibitors</td>
<td>ketoconazole, abiraterone acetate, *TAK-700 (orteronel), *VN124-1/TOK-001 (galaterone)</td>
</tr>
</tbody>
</table>

* not FDA approved
ADT for CaP Management

1. Estrogen
2. LHRH Agonist or Antagonist
3. LHRH Agonist or CAB
4. ADT to Enhance XRT
5. ADT for +PLN
6. Intermittent or Continuous ADT
7. Docetaxel and ADT
8. ADT for CRPC

CaP = Prostate cancer; CAB = combined androgen blockade; PLN = pelvic lymph nodes; CRPC = castration-recurrent prostate cancer

Diethylstilbesterol (DES)¹

1938 DES synthesized
1941 Huggins and Hodges² (Nobel Prize 1966)
1959 VACURG trials
   • CaP mortality: 1 mg = 5 mg (less CaP deaths balanced by more cardiovascular deaths)
   • Orchiectomy not improved by adding 1 or 5 mg DES
   • About 80% castrate on 1 mg and 99% on 2 mg
   • No DES dose below which cardiovascular risk is 0
1984 Leuprolide Study Group trials
   • All ADT methods = equivalent CaP response
   • Orchiectomy safer than 1 mg DES
1998 DES for second line treatment³
   • PSA response rate about 50% for about 6 months

Parenteral Estrogens

2003 Estrogen transdermal patches
- Transdermal estradiol pilot study - efficacious with excellent safety (n=20)¹

2013 PATCH trial²
- Locally advanced/metastatic CaP (n=274)
- Randomized 2:1 patch vs LHRH agonist
- Castrate T @ 3 mo: 92% patch, 93% LHRH
- CV events @ median f/u 19 mo: 10% patch, 7% LHRH
- Gynecomastia @ 6 mo: 75% patch, 19% LHRH
- Hot flashes @ 6 mo: 25% patch, 56% LHRH
- Treatment-related deaths:
  - patch = CVA @ 36 mo
  - LHRH = MI @ 2 mo
  - patch → LHRH = PE @ 16 mo
- Trial continues to OS primary endpoint


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**LHRH Agonist vs Antagonist**

1971  Shally isolates LHRH (Nobel Prize 1977)
1975  LHRH agonists developed
1985  LHRH agonists control advanced CaP
1992  LHRH antagonists developed
1998  LHRH antagonists control advanced CaP
2002  LHRH agonists and antagonists similar\(^1\)
2013  LHRHR antagonist for LHRH agonist failure
    • PSA response in 1 of 17\(^2\)


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**ADT for CaP Management**

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Combined Androgen Blockade

1984 Flutamide and leuprolide cured advanced CaP¹
1989 Flutamide enhanced PFS and OS when added to leuprolide²

Progression-free Survival
(Two-Sided P = 0.039)

Overall Survival
(Two-Sided P = 0.035)


Combined Androgen Blockade

1998 Flutamide didn’t enhance PFS or OS when added to orchiectomy¹

1995-2016 Numerous RCTs and metanalyses demonstrate little if any benefit to CAB, which increases costs and side effects of ADT

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Does XRT Make ADT More Effective?

SPCG-7/SFUO-3 Trial

- Phase III trial for locally advanced CaP
- 875 patients from 47 centers in Scandinavia: 1996-2002
  - 3 months CAB + flutamide continuously
  - 3 months CAB + RT + flutamide continuously
- Median F/U 7.6 years

- PSA Recurrence p=0.001
- CaP Deaths p=0.001
- Overall Survival p=0.004

Does ADT Make XRT More Effective?

• Neoadjuvant ADT
  • Theory: Target reduction improves oncologic control and reduces side effects
  • RTOG 86-10 (4 mo CAB)
    – 456; T2c-T4 with N1/0/x
    – Reduced PSA failure, metastases, CaP mortality
    – Trend for improved OS
    – No difference in CV mortality
  • Begin XRT in month 3 of ADT


Does ADT Make XRT More Effective?

• Adjuvant ADT
  • Theory: Controls micrometastatic disease
  • Improved overall survival demonstrated by:
    – RTOG 85-31 continuous CAB\(^1\)
      • n=977; cT3 or pT3 or N1
    – EORTC 22863 3 yrs CAB\(^2\)
      • n=415; T1-2 and GS 8-10 or T3-4 or N1
    – Harvard/DFCI 6 mo CAB\(^3\)
      • n=206; T1b-T2b and PSA >10 or GS 7-10
    – RTOG 94-08 continuous CAB\(^4\)
      • n=1979; T1b-T2b and PSA >20

[Note: RTOG 92-02 1514; T2c-4 N0 2 years CAB DFS, but not OS\(^5\)]

Fine Tune Who Needs ADT?

- RTOG 94-08 subgroup analysis by risk
  - Low (n=685): GS 6, T1-T2a, and PSA ≤10
  - Intermediate (n=1068): GS 7 or GS 6 & PSA >10-20 or T2b
  - High risk (n=226): GS 8-10

- ADT benefit not extended to low risk patients


NCCN Intermediate Risk

A New Risk Classification System for Therapeutic Decision Making with Intermediate-risk Prostate Cancer Patients Undergoing Dose-escalated External-beam Radiation Therapy

Zachary S. Zumsteg, Daniel E. Spratt, Isaac Pelt, Zhigang Zhang, Yoshia Yamada, Marisa Kollmeier, Michael J. Zelefsky

*Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; †Department of Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; ‡Department of Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA.

Available at www.sciencedirect.com
Journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority - Prostate Cancer
Editorial by Anthony V. D'Amico on pp. 903-904 of this issue
NCCN Intermediate Risk

- **Favorable Intermediate Risk**
  - Single NCCN intermediate risk factor
  - Gleason grade 3+4=7 and <50% of biopsy cores contain CaP

- **Unfavorable Intermediate Risk**
  - All others
    - Gleason primary pattern 4 or 5
    - Gleason grade 3+4=7 but ≥50% biopsy cores contain CaP
    - ≥2 NCCN intermediate risk factors


Favorable and Unfavorable NCCN Intermediate Risk Behave Differently

- PSA recurrence-free survival
- Local Recurrence
- Metastases
- CaP-specific Mortality

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ECOG Trial of Early vs Delayed ADT for pN+ CaP

T1, T2 → RP+PLND → N+  
<12 weeks: LHRH agonist or orchiectomy  
observe until progression  
n=47  
n=51

100 Enrolled 1988-93  
98 Eligible  
Follow-up median 11.9 yrs (range 9.7-14.5 for survivors)

Survival

Overall Survival

CaP-specific Survival

<table>
<thead>
<tr>
<th>ADT</th>
<th>Obs</th>
<th>Log-rank (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>47</td>
<td>51</td>
</tr>
<tr>
<td>Alive</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td>CaP recurrence-free</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>PSA failure-free</td>
<td>26</td>
<td>7</td>
</tr>
</tbody>
</table>


Population-based Test of ADT for +PLN

- SEER-Medicare 1991-1999 (PSA era)
- Propensity matched RP with N+ who received ADT <120d (n=209) after RP to those observed (n=522)
- Follow-up median 11.9 yrs (range 9.7-14.5 for survivors)

EORTC 30846: Test of ADT for +PLN

- 234 pN1-3M0 (no treatment to primary) enrolled 1986-98 and eligible for analysis
- Age 65, 93% T2/3, WHO G1 10%, 2 60%, G3 30%
- Randomized to immediate vs delayed ADT
- Median follow-up 13 yrs

<table>
<thead>
<tr>
<th></th>
<th>ADT</th>
<th>Obs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized and eligible</td>
<td>119</td>
<td>115</td>
</tr>
<tr>
<td>Alive</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>CaP death</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>CV death</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Other cause of death</td>
<td>6</td>
<td>6</td>
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Toxicities Associated with ADT

- Fatigue
- Hot flashes/hot flushes
- Loss of libido
- Osteoporosis
- Metabolic syndrome
  - Stroke
  - Myocardial infarction
  - Diabetes

Intermittent Androgen Deprivation Therapy

- Meta-analysis\(^1\) of 6 RCTs from 26 eligible (2996 men)
- Mortality similar for intermittent vs continuous ADT

SWOG 9346: Overall Survival


SWOG 9346


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SWOG 9346: Quality of Life

- At 3 months off ADT in cycle 1\(^1\)
  - Erectile function better (p<0.001)
  - Mental health better (p=0.003)
- 10 yr cumulative incidence among 636 Medicare beneficiaries:\(^2\)
  - Similar for ↑chol, osteoporosis, dementia, depression, erectile dysfunction (only 6%?)
  - Different for ischemic and thrombotic events (HR, p=0.02)
    - 24% in continuous ADT arm
    - 33% in intermittent ADT arm


SWOG 9346: Conclusions

- Non-metastatic CaP: intermittent arm
  - Perhaps small increased risk of CaP death
  - Differences in survival, if any, driven by higher Gleason scores
  - QoL better
- Metastatic CaP: intermittent arm
  - Perhaps small increased risk of CaP death
  - Differences in survival, if any, driven by symptomatic bone metastases
Can Intermittent ADT be Personalized using End-of-Induction PSA?

Mohler’s predictions
No response: survival 1 year
Good response: >90% decline in PSA (survival 3 yrs)
Excellent response: >90% decline and PSA <4.0 (± 1 yr to survival =4)
Outstanding response: >90% decline and PSA <0.2 (± 2 yrs to survival =5)

More modern
No response: PSA > 10 (survival 13 mo)
Excellent response: PSA 0.2 - <4.0 (survival 4 yrs)
Outstanding response: PSA <0.2 (survival 6 yrs)

Orchiectomy

- LHRH agonists may be dangerous used intermittently or continuously
  - LHRH receptors on heart and T lymphocytes
  - LHRH agonists affect cardiac contractility, ASVD plaque stability and inflammation
- LHRH agonists vs orchiectomy
  - Metastatic CaP without RP/XRT/anti-androgen from SEER-Medicare 1995-2009
  - 429 orchiectomy compared to 2866 LHRH agonist
  - Orch associated with
    - Lower risk of fracture, peripheral arterial disease, cardiac-related complications
    - Similar risk of diabetes, DVT/PE, Cognitive disorders

NCCN Recommendations for Metastatic CaP

- By disease-related symptoms:
  - Asymptomatic
    - Intermittent ADT
    - Discuss possible decrease in OS
    - Trade off for improved QoL during off cycle
  - Symptomatic
    - Consider continuous ADT
    - If PSA falls to <4 and certainly <0.2, intermittent ADT reasonable

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GETUG-AFU 15 Phase III Trial: ADT ± Docetaxel in Metastatic CaP

Randomized 1:1

Metastatic CaP
Kamofsky 70%
(N = 385)

ADT + docetaxel 75 mg/m² q3w for up to 9 cycles
(n = 192)

ADT
(n = 193)

- Age 64, 57% Gleason sum 8-10, 71% no local therapy, PSA 26
- Primary endpoint: OS
- 48% completed 9 cycles docetaxel although 11% required dose reduction


GETUG-AFU 15 Phase III Trial
Overall Survival

CHAARTED Phase III Trial: ADT ± Docetaxel in Metastatic CaP

Randomized 1:1

Metastatic CaP
No prior docetaxel
ECOG 0-2
(N = 790)

ADT + docetaxel 75 mg/m² q3w for up to 6 cycles
(n = 397)

ADT
(n = 393)

- Age 64, 10% AA, Gleason sum 8-10 in 2/3, 73% no local therapy, PSA 51
- Primary endpoint: OS
- 86% completed 6 cycles docetaxel although 26% required dose reduction


Overall Survival

High volume disease: visceral metastases and/or ≥4 bone metastases (≥1 outside the pelvis or vertebral column)

High Volume

Low Volume

**STAMPEDE**

- Adaptive, multi-arm, multi-stage, platform randomized, controlled Phase II/III
- Arms filled 2:1:1:1
  - ADT (n=1184)
  - ADT+zoledronic acid (n=593)
  - ADT+6 cycles docetaxel (n=592)
  - ADT+ZA+Doc (n=593)
- Research subjects
  - M+, N+, high risk locally advanced (≥2 of T3/4, GS 8-10, and PSA ≥40)
  - RP/XRT failure with ≥1 of PSA ≥4 and PSADT <6 mo, PSA ≥20, N+ or M+
- XRT to primary encouraged for N0M0 until 2011 then mandated; XRT optional for N+M0

**STAMPEDE**

- Age 65, Gleason sum 8-10 in 3/4, PSA 63
- Primary endpoint: OS
- 90% power at 1-sided α=0.025 to detect 25% improvement in OS once ADT only control arm has 400 deaths; 3 interim analyses for lack of benefit on failure-free survival
- 74% completed 6 cycles docetaxel; 10% never started; dose reduction?
- Grade 3-5 toxicity
  - Doc or Doc-ZA arms 52%
  - ADT or ADT-ZA arms 32%

**STAMPEDE**

**Failure-free Survival**  
Overall Survival

*STAMPEDE*  

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**STAMPEDE**

Forest Plots of Treatment Effect on Survival within Subsets

*STAMPEDE*  
Effect on Overall Survival of Adding Docetaxel to Standard of Care

• Systematic review identified 5 RCTs in M1 and 11 RCTs in M0
• Meta-analysis of 3206 M1 patients from 3 RCTs and 3978 M0 patients from 3 RCTs

NCCN Recommendations for Metastatic CaP

• By disease-related symptoms:
  – Asymptomatic
    • Intermittent ADT
    • Discuss possible decrease in OS
    • Trade off for improved QoL during off cycle
  – Symptomatic
    • Consider continuous ADT
    • If PSA falls to <4 and certainly <0.2, intermittent ADT reasonable
  – Younger and healthier - docetaxel 6 cycles + ADT
  – Older and/or unhealthier - ADT

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**Androgen Receptor (AR) Expression in Castration-Recurrent CaP**

- androgen-stimulated benign prostate
- castration-recurrent CaP

**AR Hypersensitized**

- AR 10,000 times more sensitive in androgen-independent than androgen-sensitive CaP cell lines\(^1\)
- AR coactivators change from SRC-1 to TIF-2 in cell lines,\(^1\) xenografts,\(^1\) and clinical specimens\(^2\)
- AR phosphorylated by SRC\(^3\) or Ack\(^1\) tyrosine kinases


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**Inactivate AR using Antiandrogens**

- Old and relatively ineffective
  - Flutamide
  - Bicalutamide
  - Nilutamide
- New and perhaps more effective
  - Small molecule AR antagonist (enzalutamide)
  - AR-specific histone deacetylase inhibitors
    - Vorinostat, panobinostat, romidepsin
Enzalutamide

- 1199 men with CRPC after docetaxel
- 2:1 MDV3100 160 mg qd vs placebo
- Stopped at interim analysis after 520 deaths
- Overall survival (primary endpoint)
  - MDV3100 18.4 mo
  - Placebo 13.6 mo
- All secondary endpoints met, i.e., time to PSA progression
  - MDV3100 8.3 mo
  - Placebo 3.0 mo
- Side effects
  - 0.6% seizures
  - Fatigue, diarrhea, hot flashes


Enzalutamide vs Bicalutamide

- International randomized, double-blind Phase II study (TERRAIN)
- 375 men with metastatic castration-recurrent CaP enrolled Mar 2011-July 2013
- 1:1 160 mg/d Enz or 50 mg/d Bic
- 1° endpoint: Progression-free survival
- Side effects
  - 1 seizure in each arm
  - Tx discontinued 8% Enz vs 5% Bic
  - Grade ≥3 9% Enz vs 8% Bic
- QoL
  - Fact P improved at a higher rate in most domains for Enz vs Bic

Enzalutamide vs Bicalutamide


Tissue Androgen Levels using Radioimmunoassay in Benign Prostate (n = 32; gray) vs Castration-Recurrent CaP (n = 23; white)

Origin of Tissue Dihydrotestosterone (DHT) in Castration-Recurrent CaP

Adrenal androgen pathway
Cholesterol pathway
Backdoor pathway

Pathways to DHT Synthesis

Intact pathway
Adrenal androgen pathway
Cholesterol pathway
Backdoor pathway

CYP17A1 Inhibition

- Abiraterone
  - Attard, J Clin Oncol, 2008
- TAK-700
  - Kaku, Bioorg Med Chem, 2011
- VN124-1
  - Handratta, J Steroid Biochem Mol Biol, 2004
  - Vasaitis, Mol Cancer Ther, 2008

Pre-docetaxel: Overall Survival Favors Abiraterone but Pre-specified Boundary not Crossed

- **Abiraterone**
  - Median, mos: 35.3
- **Prednisone**
  - Median, mos: 30.1

HR (95% CI): 0.79 (0.66-0.96)
p Value*: 0.0151

IA3 data. *Prespecified significance level by O’Brien-Fleming Boundary = 0.0035.

After Docetaxel: Abiraterone Improves Overall Survival

HR=0.646 (0.54-0.77)  \( P <0.0001 \)

Abiraterone: 14.8 months (95% CI: 14.1, 15.4)
Placebo: 10.9 months (95% CI: 10.2, 12.0)

1 Prior Chemo OS:
15.4 months abiraterone vs 11.5 months placebo

Mechanisms for Abiraterone Resistance

Reported mechanisms for resistance based on in vitro studies include:

- progesterone accumulation to overcome competitive inhibition by abiraterone\(^1,2\)
- CYP17A1 gene amplification\(^1\)
- alternate pathways for DHT metabolism\(^2\)
- development of AR mutants or splice variants\(^3\)

Hypothesis: Abiraterone inhibits CYP17A1 that may be too far from DHT synthesis to achieve long term response by inhibition.

Overview of Current Main Treatment Options for Castration-Recurrent CaP

<table>
<thead>
<tr>
<th>Nonmetastatic</th>
<th>Metastatic, asymptomatic/min sx</th>
<th>Metastatic chemotherapy naive</th>
<th>Metastatic, post docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-line hormonal therapy</td>
<td>Abiraterone</td>
<td>Docetaxel</td>
<td>Abiraterone</td>
</tr>
<tr>
<td></td>
<td>Enzalutamide</td>
<td>Radium-223</td>
<td>Enzalutamide</td>
</tr>
<tr>
<td></td>
<td>Sipuleucel-T</td>
<td>Abiraterone</td>
<td>Cabazitaxel</td>
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<tr>
<td></td>
<td></td>
<td>Enzalutamide</td>
<td>Radium-223</td>
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<td></td>
<td></td>
<td>Strontium 89</td>
<td>Sipuleucel-T</td>
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<td></td>
<td></td>
<td>Samarium 153</td>
<td>Mitoxantrone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitoxantrone</td>
<td></td>
</tr>
</tbody>
</table>

- Green: Extends survival time (level 1 evidence)
- Orange: Pain palliation only (level 1 evidence)
- Blue: No level 1 evidence for outcome benefit


How much do the new CRPC agents cost?

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### Cost of Survival using New CRPC Agents

<table>
<thead>
<tr>
<th>Treatment</th>
<th>FDA Approval</th>
<th>Cost</th>
<th>Added Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 cycles of Docetaxel</td>
<td>05/19/2004</td>
<td>$78,000</td>
<td>2.4</td>
</tr>
<tr>
<td>1 course of Sipuleucel-T</td>
<td>04/26/2010</td>
<td>$110,000</td>
<td>4.1</td>
</tr>
<tr>
<td>8 mo Abiraterone</td>
<td>12/10/2012</td>
<td>$46,000</td>
<td>4.0</td>
</tr>
<tr>
<td>8 mo Enzalutamide</td>
<td>08/31/2012</td>
<td>$64,000</td>
<td>4.8</td>
</tr>
<tr>
<td>6 cycles of Cabazitaxel</td>
<td>06/17/2010</td>
<td>$168,000</td>
<td>2.4</td>
</tr>
<tr>
<td>1 course of Rad-223</td>
<td>05/15/2013</td>
<td>$66,000</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>$532,000</strong></td>
<td><strong>23.3</strong></td>
</tr>
</tbody>
</table>

Assumptions: drug stopped at mean time to progression, and patient realizes mean extension of survival reported in Phase III trials, and patient completes the planned courses of Sipuleucel-T (2 treatments) and Rad-223 (6 treatments).

### ADT for CaP Management

1. Estrogen  Try parenteral?
2. LHRH Agonist or Antagonist  Doesn’t matter
3. LHRH Agonist or CAB  Doesn’t matter
4. ADT to enhance XRT  High risk: Yes  Intermediate Favorable: No  Intermediate Unfavorable: Maybe
5. ADT for +PLN  Maybe
6. Intermittent or Continuous ADT  Intermittent first
7. Docetaxel and ADT  Docetaxel in healthy men esp. if high vol. M+
8. New agents for ADT for CRPC  Yes but sequence unclear