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

James Mohler, MD

Roswell Park Cancer Institute

National Comprehensive Cancer Network®

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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!

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

* 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 Hodges[2] (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 treatment[3]
- PSA response rate about 50% for about 6 months

1. Turo R, et al. Scand J Urol 2014;48:4-14.
2. Huggins C, Hodges CV. Cancer Res 1941;1:293-7.
3. Smith DC, et al. Urology 1998;52:257-60.

Parenteral Estrogens

2003 Estrogen transdermal patches

- Transdermal estradiol pilot study - efficacious with excellent safety (n=20)[1]

2013 PATCH trial[2]

- 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

1. Ockrim JL, et al. J Urol 2003;169:1735-7.
2. Langley RE, et al. Lancet Oncol 2013;14:306-16.

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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 LRHR antagonist for LHRH agonist failure

- PSA response in 1 of 17[2]

1. Trachtenberg, et al. J Urol 2002;167:1670-4.
2. Masson-Lecomte A, et al. World J Urol 2013;31:339-43.

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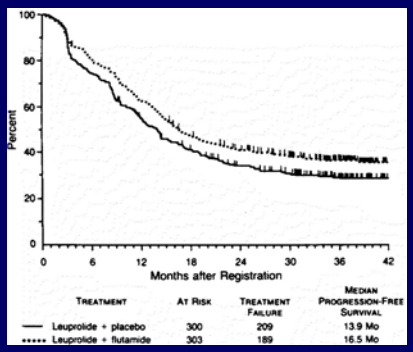
Combined Androgen Blockade

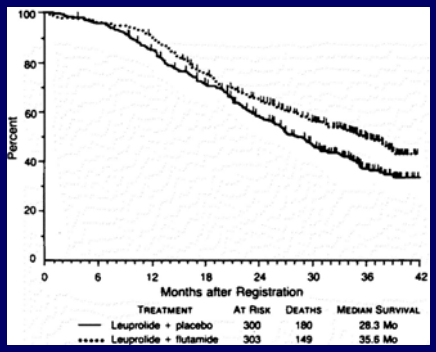
1984 Flutamide and leuprolide cure advanced CaP[1]

1989 Flutamide enhanced PFS and OS when added to leuprolide[2]

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



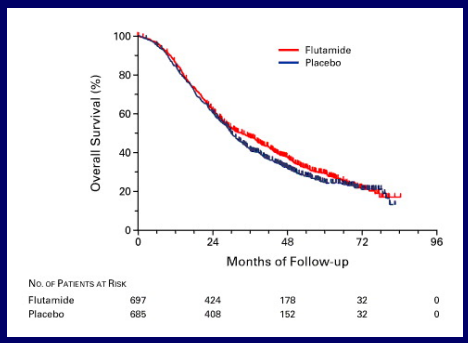
Overall Survival
(Two-Sided P = 0.035)



1. Labrie F, et al. Lancet 1984;2:1090.
2. Crawford ED, et al. N Engl J Med 1989;321:419-24. Erratum in: N Engl J Med 1989;321:1420.

Combined Androgen Blockade

1998 Flutamide didn't enhance PFS or OS when added to orchiectomy[1]



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

1. Eisenberger M, et al. N Engl J Med 1998;339:1036-42.

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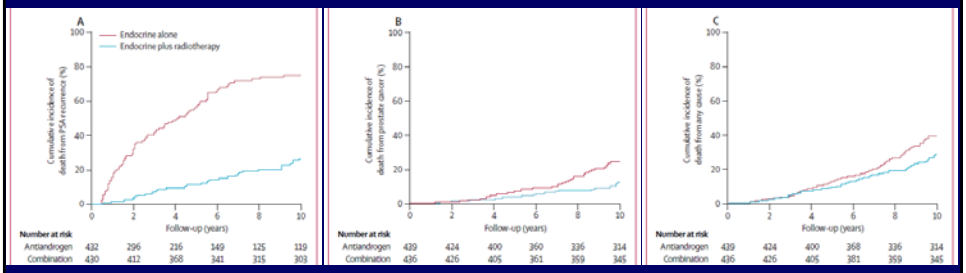
Does XRT Make ADT More Effective?

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	CaP Deaths	Overall Survival
p=0.001	p=0.001	p=0.004

Widmark, et al. Lancet 2009;373:301-8.

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

Roach, et al. J Clin Oncol 2008;26:585-91.

Does ADT Make XRT More Effective?

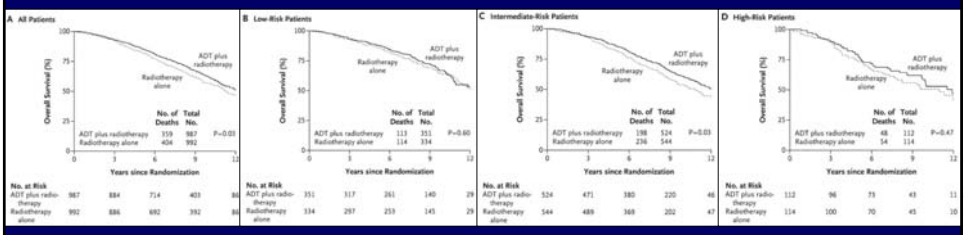
- Adjuvant ADT
- Theory: Controls micrometastatic disease
- Improved overall survival demonstrated by:
  - RTOG 85-31 — continuous CAB[1]
    - n=977; cT3 or pT3 or N1
  - EORTC 22863 — 3 yrs CAB[2]
    - n=415; T1-2 and GS 8-10 or T3-4 or N1
  - Harvard/DFCI — 6 mo CAB[3]
    - n=206; T1b-T2b and PSA >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]

1. Pilepich MV, et al. Int J Radiat Oncol Biol Phys. 2005;61:1285-90.
2. Bolla M, et al. N Engl J Med. 1997;337:295-300.
3. D'Amico AV, et al. JAMA. 2015;314:1291-3.
4. Jones CU, et al. N Engl J Med. 2011;365:107-18.
5. Hanks GE, et al. J Clin Oncol. 2003;21:3972-8.

Fine Tune Who Needs ADT?

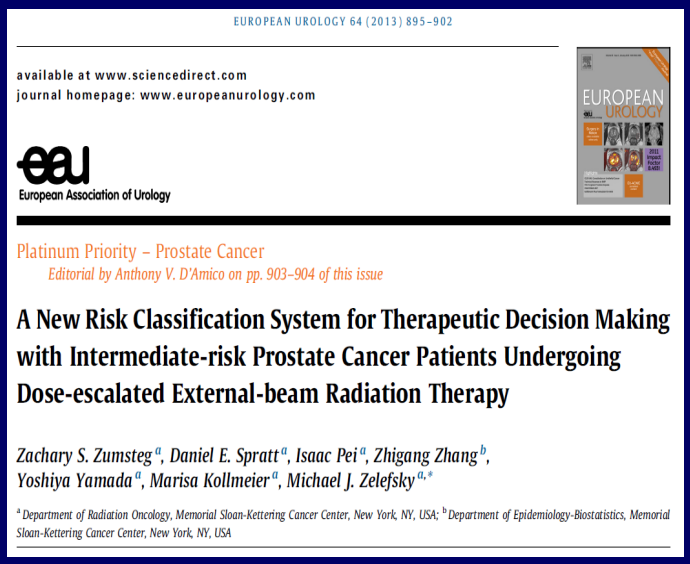
- RTOG 94-08 subgroup analysis by risk
  - Low (n=685): GS 6, T1-T2a, and PSA ≤10
  - Intermediate (n=1068): GS 7 or GS 6 & PSA >10-20 or T2b
  - High risk (n=226): GS 8-10



- ADT benefit not extended to low risk patients

Jones CU, et al. N Engl J Med 2011;365:107-18.

NCCN Intermediate Risk



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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

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[a], Daniel E. Spratt[a], Isaac Pei[a], Zhigang Zhang[b], Yoshiya Yamada[a], Marisa Kollmeier[a], Michael J. Zelefsky[a,]*

[a] Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [b] Department of Epidemiology-Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

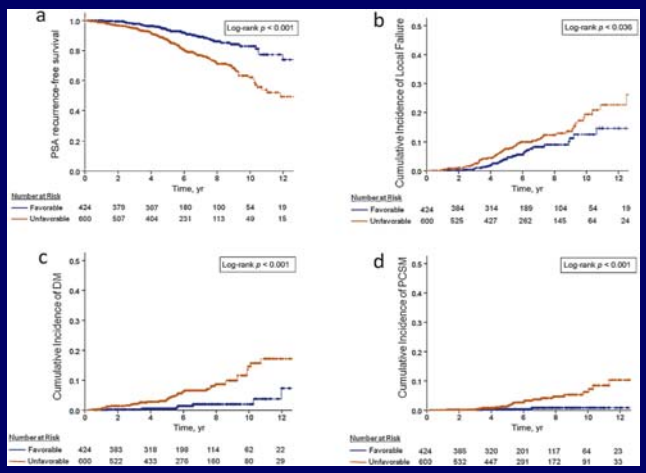
NCCN Intermediate Risk

- 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

Zumsteg ZS, et al. Eur Urol 2013;64:895-902.

Favorable and Unfavorable NCCN Intermediate Risk Behave Differently

PSA recurrence-free survival Local Recurrence



Metastases CaP-specific Mortality

Zumsteg ZS, et al. Eur Urol 2013;64:895-902.

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ECOG Trial of Early vs Delayed ADT for pN+ CaP

T1, T2 → RP+PLND → N+

n=47 → <12 weeks: LHRH agonist or orchiectomy

n=51 → observe until progression

100 Enrolled 1988-93

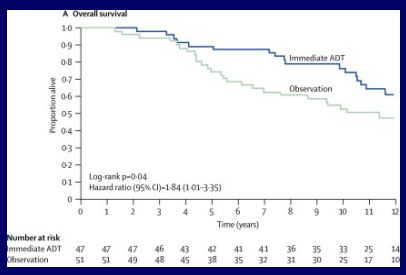
98 Eligible

Follow-up median 11.9 yrs (range 9.7-14.5 for survivors)

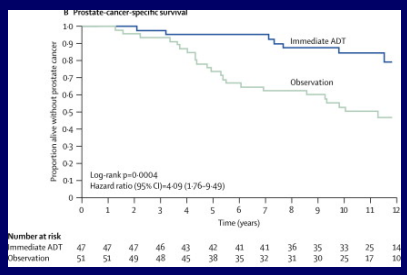
Messing E, et al. N Engl J Med 1999;341:1781-8; Messing E, et al. Lancet Oncol 2006;7:472-9.

Survival

Overall Survival



CaP-specific Survival



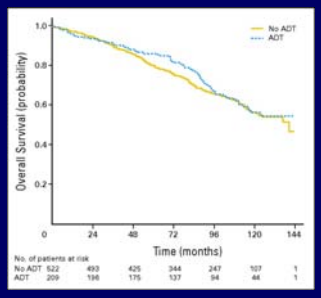
	ADT	Obs	Log-rank (p)
Randomized	47	51	
Alive	30	23	0.04
CaP recurrence-free	29	12	<.0001
PSA failure-free	26	7	<.0001

Messing E, et al. Lancet Oncol 2006;7:472-9

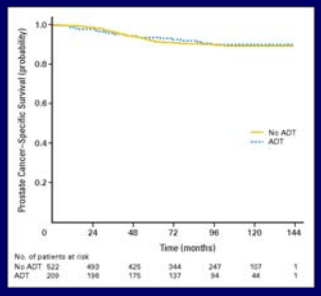
Population-based Test of ADT for +PLN

- 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)

Overall Survival



CaP-specific Survival



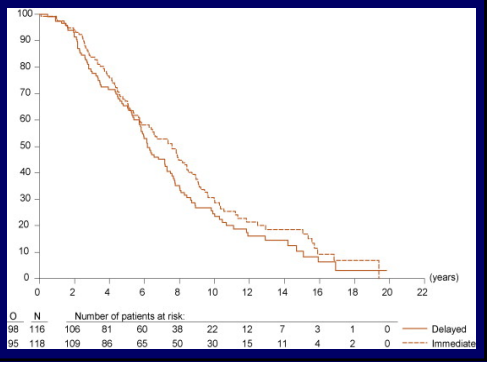
Wong YN, et al. J Clin Oncol 2008;27:100-5

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

	ADT	Obs
Randomized and eligible	119	115
Alive	23	18
CaP death	69	70
CV death	10	10
Other cause of death	6	6

Overall Survival



Schroder FH, et al. Eur Urol 2009;55:14-22

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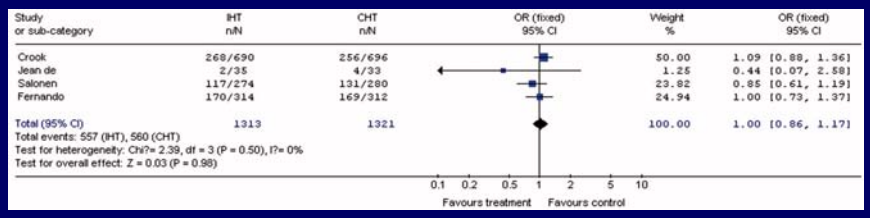
Toxicities Associated with ADT

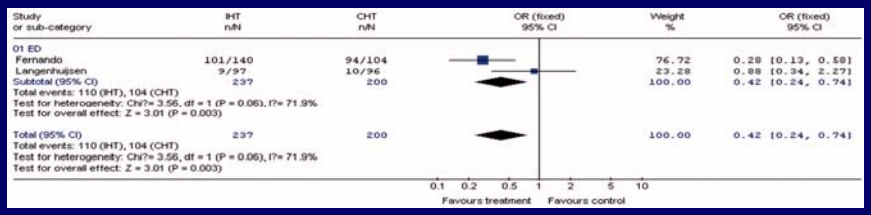
- Fatigue
- Hot flashes/hot flushes
- Loss of libido
- Osteoporosis
- Metabolic syndrome
  - Stroke
  - Myocardial infarction
  - Diabetes

Intermittent Androgen Deprivation Therapy

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

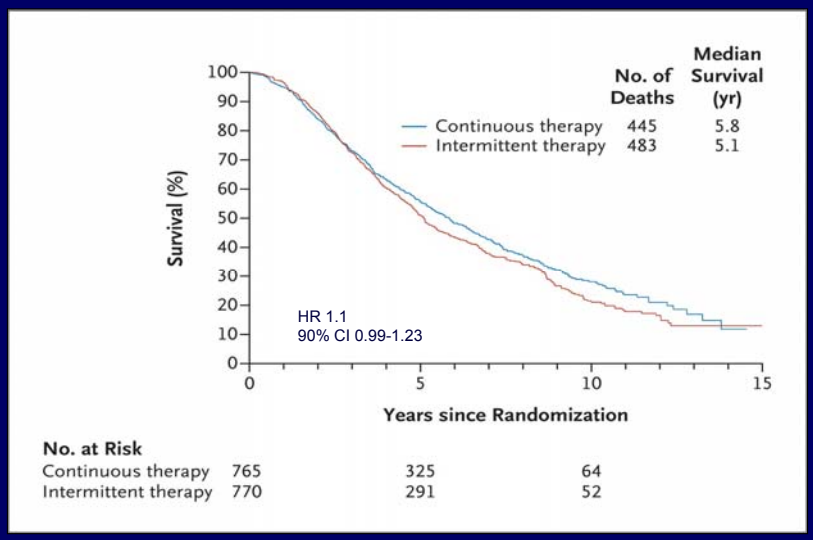


- QoL better for intermittent vs continuous ADT (example, erectile dysfunction)

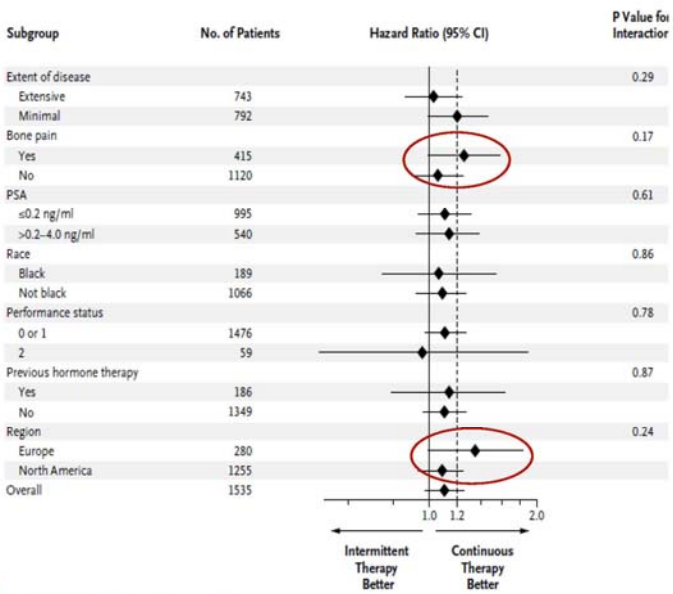


1. Dong Z, et al. Aging Male 2015;18:233-7.

SWOG 9346: Overall Survival



Hussain M, et al. N Engl J Med 2013;368:1314-25; slide courtesy of Dr. Hussain



SWOG 9346

Hussain M, et al. N Engl J Med 2013;368:1314-25; slide courtesy of Dr. Hussain

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

1. Hussain M, et al. N Engl J Med 2013;368:1314-25.
2. Hershman DL, et al. JAMA Oncol 2015; published online Dec. 23, 2015

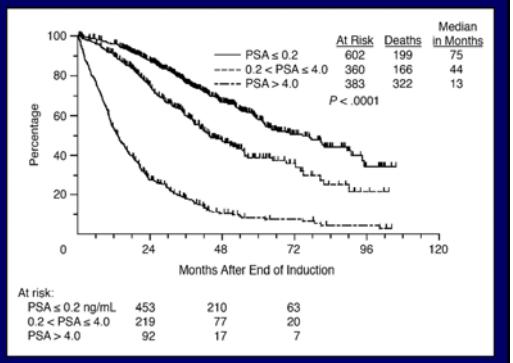
SWOG 9346: Conclusions

- 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[1]
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)



1. Hussain M, et al. J Clin Oncol 2006;24:3984-3990.

Orchiectomy

- LHRH agonists may be dangerous used intermittently or continuously[1]
  - LHRH receptors on heart and T lymphocytes
  - LHRH agonists affect cardiac contractility, ASVD plaque stability and inflammation
- LHRH agonists vs orchiectomy[2]
  - 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

1. Sun, et al. JAMA Oncol 2015; published online Dec. 23, 2015.
2. Kolinsky, et al. JAMA Oncol 2015; published online Dec. 23, 2015.

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
Karnofsky 70%
(N = 385)

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

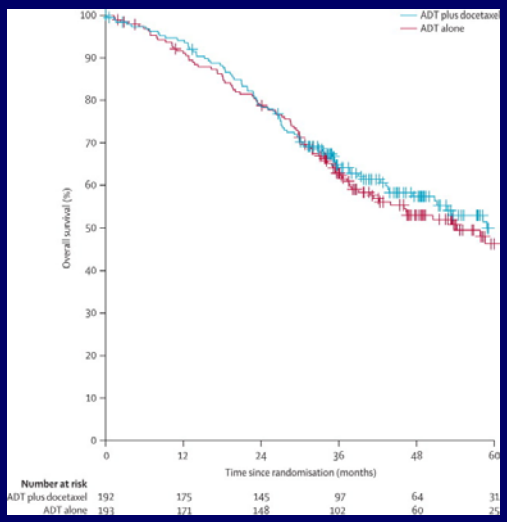
ADT
(n = 193)

- 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

Gravis G, et al. Lancet Oncol 2013;14:149-58.

GETUG-AFU 15 Phase III Trial

Overall Survival



Gravis G, et al. Lancet Oncol 2013;14:149-58.

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)

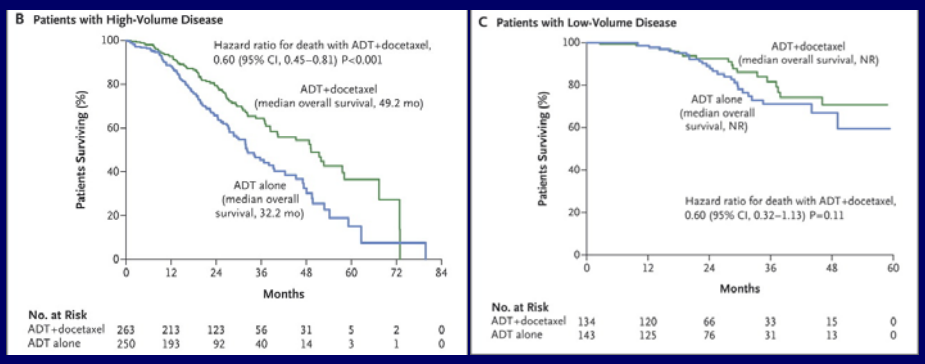
- Age 64, 10% AA, Gleason sum 8-10 in 2/3, 73% no local therapy, PSA 51
- Primary endpoint: OS
- 86% completed 6 cycles docetaxel although 26% required dose reduction

Sweeney CJ, et al. N Engl J Med 2015;373:737-746.

Overall Survival

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

High Volume | Low Volume



Sweeney CJ, et al. N Engl J Med 2015;373:737-746.

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

James ND, et al. Lancet 2015; published online Dec 21, 2015.

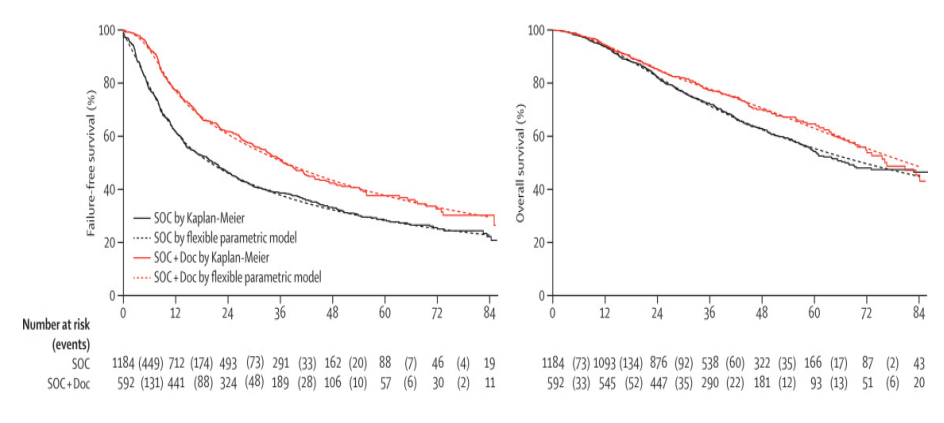
STAMPEDE

- 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%

James ND, et al. Lancet 2015; published online Dec 21, 2015.

STAMPEDE

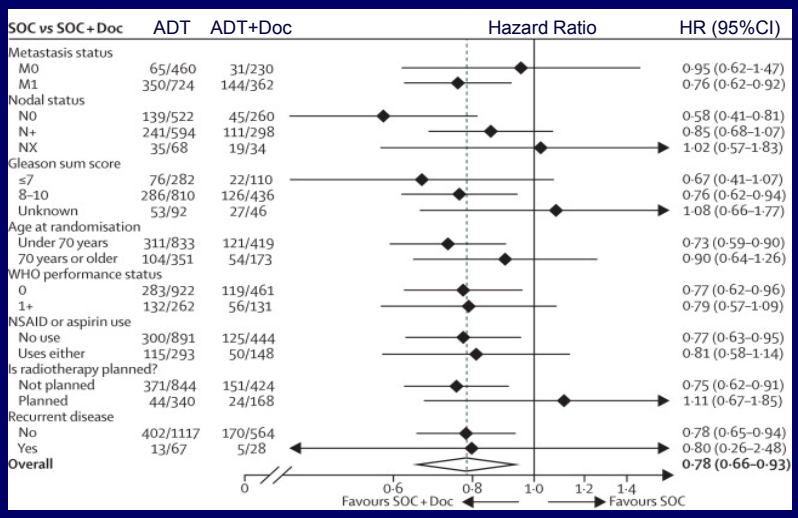
Failure-free Survival | Overall Survival



James ND, et al. Lancet 2015; published online Dec 21, 2015.

STAMPEDE

Forest Plots of Treatment Effect on Survival within Subsets

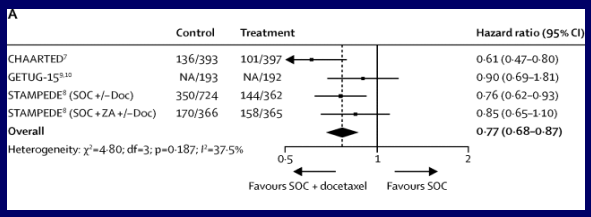


James ND, et al. Lancet 2015; published online Dec 21, 2015.

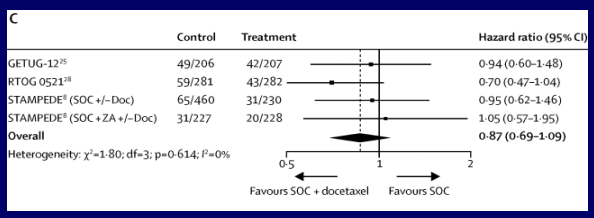
Effect on Overall Survival of Adding Docetaxel to Standard of Care

- 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

M1



M0



Vale CL, et al. Lancet Oncol 2016;17:243-56.

NCCN Recommendations for Metastatic CaP

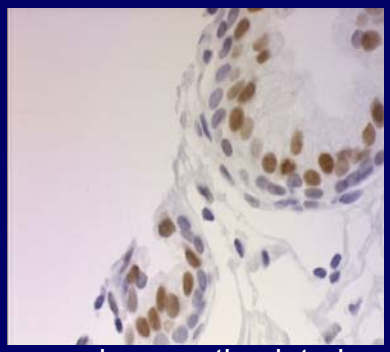
- By disease-related symptoms:
  - Asymptomatic
    - Intermittent ADT
    - Discuss possible decrease in OS
    - Trade off for improved QoL during off cycle
  - Symptomatic
    - Consider continuous ADT
    - If PSA falls to <4 and certainly <0.2, intermittent ADT reasonable
- By age and co-morbidities: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

ADT for CaP Management

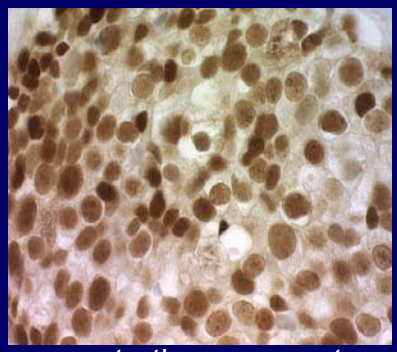
1. Estrogen
2. LHRH Agonist or Antagonist
3. LHRH Agonist or CAB
4. ADT to Enhance XRT
5. ADT for +PLN
6. Intermittent or Continuous ADT
7. Docetaxel and ADT
8. ADT for CRPC

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

Androgen Receptor (AR) Expression in Castration-Recurrent CaP



androgen-stimulated benign prostate



castration-recurrent CaP

Mohler JL, et al. Clin Cancer Res 2004;10:440-8.

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 Ack1[4] tyrosine kinases

1. Gregory CW, et al. Cancer Res 2001;61:2892-98.
2. Agoulnik IU, et al. Cancer Res 2006;66:1054-60.
3. Guo Z, et al. Cancer Cell 2006;10:309-19.
4. Mahajan NP, et al. Proc Natl Acad Sci USA 2007;104:8438-43.

Inactivate AR using Antiandrogens

- Old and relatively ineffective
  - Flutamide
  - Bicalutamide
  - Nilutamide
- New and perhaps more effective
  - Small molecule AR antagonist (enzalutamide)
    - Tran C, et al. Science 2009;324:787-90.
    - Scher HI, et al. N Engl J Med 2012;367:1187-97.
  - AR-specific histone deacetylase inhibitors
    - Vorinostat, panobinostat, romidepsin
    - ie, Welsbie DS, et al. Cancer Res 2009;69:958-66.

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, ie time to PSA progression
  - MDV3100 8.3 mo
  - Placebo 3.0 mo
- Side effects
  - 0.6% seizures
  - Fatigue, diarrhea, hot flashes

Scher HI, et al. N Engl J Med 2012;367:1187-97

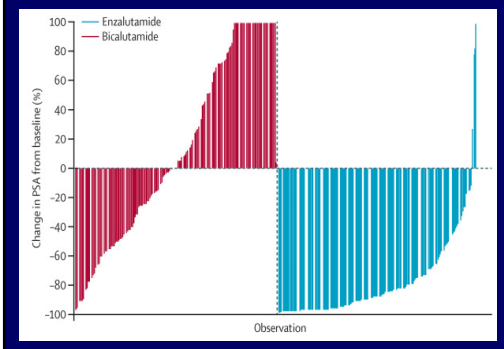
Enzalutamide vs Bicalutamide

- 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

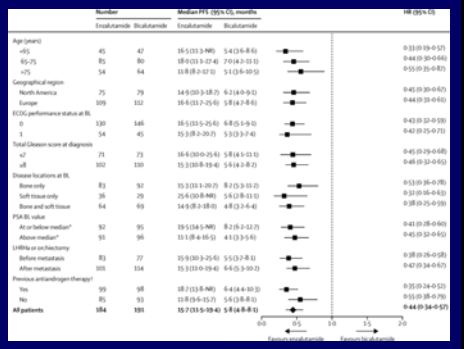
Shore ND, et al. Lancet Oncol 2016;17:153-63.

Enzalutamide vs Bicalutamide

PSA Waterfall Plot

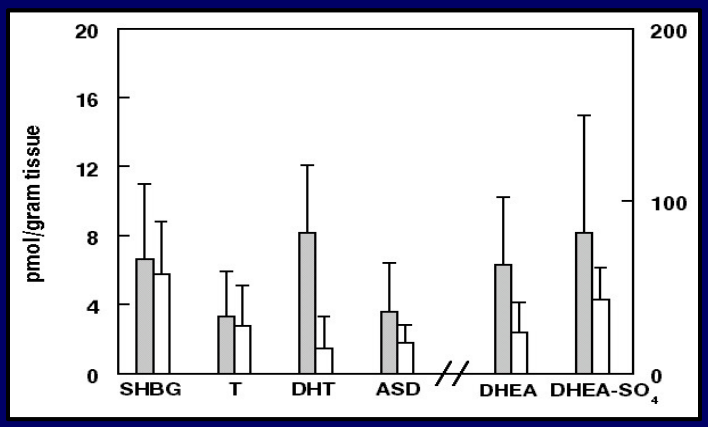


Progression-Free Survival



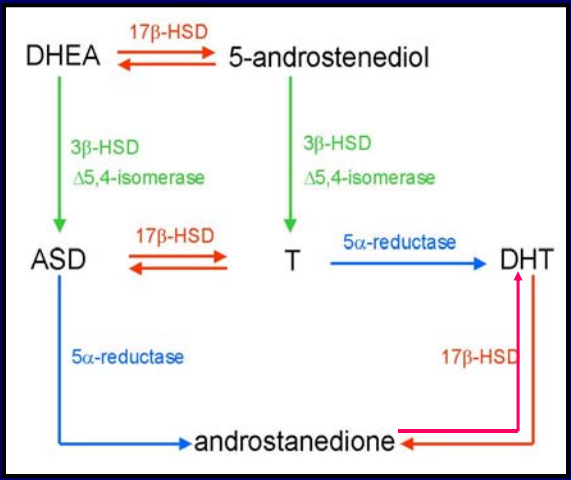
Shore ND, et al. Lancet Oncol 2016;17:153-63.

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



Mohler JL, et al. Clin Cancer Res 2004;10:440-8.

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



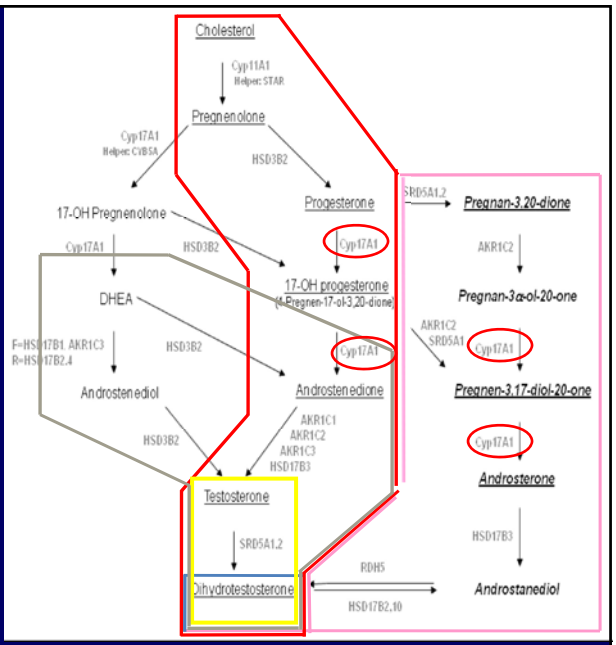
Pathways to DHT Synthesis

Intact pathway

Adrenal androgen pathway

Cholesterol pathway

Backdoor pathway

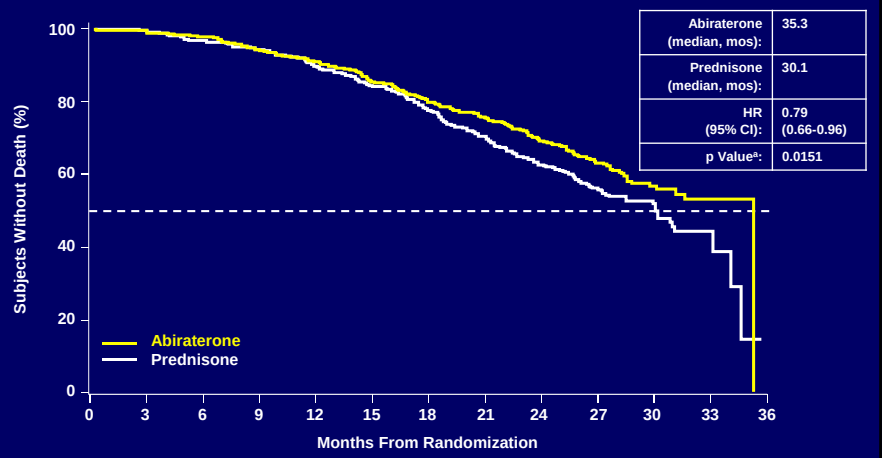


Modified from Locke, Cancer Res 2008;68:6407-15.

CYP17A1 Inhibition

- Abiraterone
  - Attard, J Clin Oncol, 2008
- TAK-700
  - Yamaoka, J Steroid Biochem Mol Biol, 2012
  - 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[a]:	0.0151

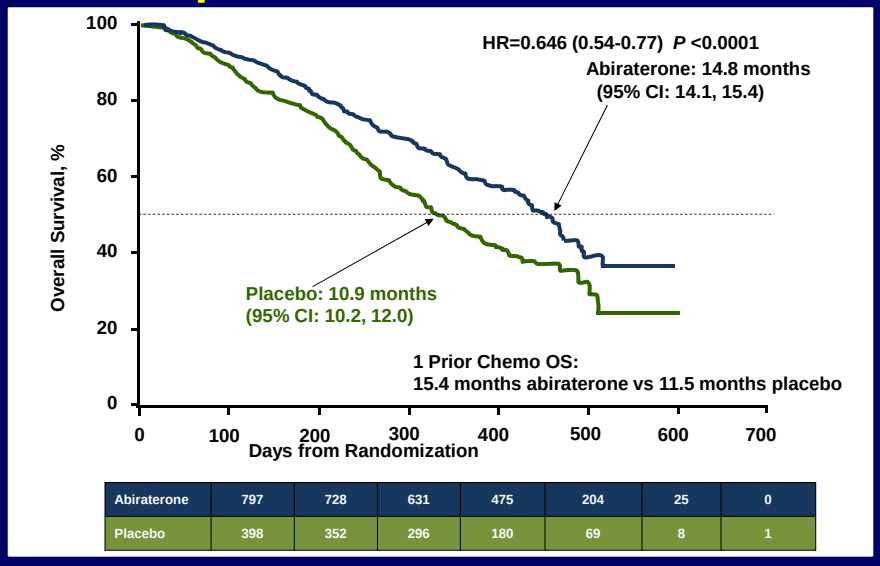
Abiraterone	546	538	524	503	482	452	421	393	333	175	68	15	0
Prednisone	542	534	508	492	465	437	400	361	283	153	67	9	0

IA3 data. [a]Prespecified significance level by O'Brien-Fleming Boundary = 0.0035.

Ryan C, et al. N Engl J Med 2013;368:138-48; updated at GU ASCO 2013

P. Kantoff

After Docetaxel: Abiraterone Improves Overall Survival



Abiraterone	797	728	631	475	204	25	0
Placebo	398	352	296	180	69	8	1

de Bono JS, et al. N Engl J Med 2011;364:1995-2005.

Courtesy of P. Kantoff

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.

1. Cai C, et al. Cancer Res 2011;71:6503-13.
2. Titus MA, et al. Prostate 2014;74:235-49.
3. Mostaghel EA, et al. Clin Cancer Res 2011;17:5913-25

Overview of Current Main Treatment Options for Castration-Recurrent CaP

Nonmetastatic	Metastatic, asymptomatic/min sx	Metastatic chemotherapy naive	Metastatic, post docetaxel
Second-line hormonal therapy	Abiraterone	Docetaxel	Abiraterone
	Enzalutamide	Radium-223	Enzalutamide
	Sipuleucel-T	Abiraterone	Cabazitaxel
		Enzalutamide	Radium-223
		Strontium 89	Sipuleucel-T
		Samarium 153	Mitoxantrone
		Mitoxantrone	

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

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How much do the new CRPC agents cost?

Cost of Survival using New CRPC Agents

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

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